# AUTONOMIC IMBALANCE *and the* HYPOTHALAMUS

## *IMPLICATIONS FOR PHYSIOLOGY, MEDICINE, PSYCHOLOGY, AND NEUROPSYCHIATRY*

**ERNST GELLHORN, M.D., Ph.D.**

# *Autonomic Imbalance and the Hypothalamus*

. . . human truths, however valuable they may seem, are always open to challenge, to revision, to refinement, to refutation, to repeal. Only the quest is eternal.

A. Guérard, *Bottle in the Sea* (1954)

Happiness consists in devotion to a dream or to a duty.

E. Renan, *Recollections of My Youth*

# AUTONOMIC IMBALANCE *and the Hypothalamus*

## IMPLICATIONS FOR PHYSIOLOGY, MEDICINE PSYCHOLOGY, AND NEUROPSYCHIATRY

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*To*

*Mr. A. A. Heckman, Executive Director,*
*and to the Board of Directors, of the*
*Louis W. and Maud Hill Family Foundation*

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# PREFACE

Only lunatics can be completely original.

Will Durant, *The Age of Faith* (1950)

THE experiments described in this monograph had their origin in the clinical observation of Funkenstein, Greenblatt, and Solomon that the intensity of the hypotensive action of mecholyl showed greater variations in neuropsychiatric patients than in controls, and particularly in the fact that this effect of the drug changed with the change in the mental condition of the patient. This finding was illustrated in a number of publications, but not evaluated in its theoretical significance.

In view of my earlier studies on the relation between the diencephalon and psychic disorders (86, 87, 90, 94), the original observation of Funkenstein *et al.* suggested to me the possibility of measuring the excitability of the hypothalamus in the intact organism through autonomic tests. Since this idea would have far-reaching consequences for clinical medicine and neuropsychiatry, the problem was attacked on a broad basis. The experiments proving the validity of the idea, the application of the underlying principle to the parasympathetic system, and the results obtained with these tests in normal persons and psychiatric patients, are reported in this monograph. In addition, it became necessary to subject the closely related problem of autonomic imbalance and its ramifications (including hypothalamic-cortical relations, somato-autonomic integration, and homeostasis) to an experimental analysis.

If it is correct that a disturbance of functions is the first observable sign of the disease process long before an anatomical lesion appears, the physician must be interested in the physiological analysis of functional changes and abnormal reactions of the autonomic nervous system which seem to throw some light on numerous clinical problems. In view of the central role which the hypothalamus plays in the physiology of the emotions and behavior, psychologists and neuropsychiatrists, it is hoped, will find the studies reported in this book of value in solving their problems.

*Readers who are not well acquainted with neurophysiological research or cannot spare the time to read the detailed report of the* *physiological experiments and their evaluation are advised to substitute pp. 217–221, 225–228, and 239–242 for Chapters 1, 2, and 7.* An attempt has been made to correlate the experimental findings with medical, psychiatric, and psychological problems, in the hope of stimulating further research.

Although the major part of the experimental work reported in this book has been performed during the last few years, its roots go back to my student days when, under the influence of my teachers in the medical sciences and the humanities, my interest in the nervous system was aroused and the ideals took shape which have guided me through the vicissitudes of academic life and through personal tragedy. Neurophysiology, when seen in its larger aspects, is charged with the task of explaining the mind, and yet it is deeply rooted in the natural and biological sciences. Its area lies at the crossroads between the sciences and the humanities, separated at the present time by an ever widening gulf. In these circumstances it is perhaps not superfluous for a teacher, at the end of his career, to make a profession for the sake of the younger generation: first, to acknowledge his indebtedness not only to the teachers of physiology who influenced his scientific goals but also to the representatives of the humanities who helped him to develop his personality; secondly, to express his desire that these sources of information and moral strength should be utilized to a greater extent than today in the education of scientists. "The very summit of man's achievement," said Goethe, "is the capacity to marvel." "Wonder," writes J. Pieper, in quoting these words, "is the *principium*, the lasting source, the *fons et origo*, the immanent origin of philosophy." Of experimental science the same could be said. Indeed one might even say that the fundamental, perhaps the physiological, basis of the creative act is the same, whether in philosophy, the arts, or the sciences. What Pieper writes about philosophy, that "the joy that accompanies wonder is the joy of the mind and spirit that is always open to what is fresh, new, and as yet unknown," is just as applicable to science. In the sciences as well as in the humanities, should not the teacher by his enthusiasm, checked of course by rigorous criticism but undaunted by failure, attempt to transmit this joy and this wonder to the younger generation? If he could do so, then a generation of humanistic scientists might develop who would not recognize a schism between scientific and humanistic endeavors. On the contrary, they would attempt, in their life and work, to reconcile these main foundations of the creative life. Such scientific humanists would agree with Goethe, "Das Leben ist keine Lust, das Leben ist aber auch keine Last; das Leben ist eine Aufgabe,"* and act according to the precepts of Euripides:

> When you are about to take some action by your-
>   self, call then on the powers above.
> For divinity also takes a hand to help him who tries
>   to help himself.

My thanks are due to the Hill Family Foundation and its executive director, Mr. A. A. Heckman, who made the present work possible; to the President and Regents of the University of Minnesota for a short leave and a sabbatical leave used to write the monograph; to my collaborators H. M. Ballin, W. P. Koella, H. Nakao, R. Nelson, E. S. Redgate, and T. Tokizane for their devotion to the work.

I am deeply grateful to my friends for reading the manuscript, and particularly to Dr. G. N. Loofbourrow for his keen criticism; to Mrs. Vera Clausen of the Biomedical Library of the University of Minnesota for her continued cooperation; to the staff of the University of Minnesota Press, and especially to my friend Dr. Doris Franklin, for unfailing help.

A large part of the experimental and clinical material in this book is presented here for the first time. Of its 101 illustrations, 70 are from unpublished investigations. The author wishes to express his grateful appreciation to the editors and publishers of the *Journal of Neurophysiology*, *EEG, Clin. Neurophysiol.*, *Journal of Physiology*, and *Arch. Internat. Pharmacodyn.* for permission to reprint illustrations from these journals.

E. GELLHORN

*2 Fellowship Circle*
*Santa Barbara, California*
*December 1956*

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* "Life is no pleasure, but neither is it a burden; life is a task."—The quotations from Pieper are from his book *Leisure, the Basis of Culture* (1952). According to information kindly supplied by Professor W. Jaeger of Harvard, the lines from Euripides are from the lost version of the *Hippolytus*.

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# *Autonomic Imbalance and the Hypothalamus*

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# INTRODUCTION

IT IS a long-established fact based on experiments on various nerve-muscle preparations that a given stimulus acting on an autonomically innervated organ produces diametrically opposed effects on this organ in different physiological states. Thus, stimulation of the hypogastric nerve elicits a relaxation of the virginal uterus but a contraction of the pregnant uterus of the cat (49), and the smooth muscles of the gastro-intestinal tract react to various stimuli differently in different states of tone.

Without adding further examples, it may be said that fundamental alterations and even a reversal in the responsiveness of autonomically innervated structures have frequently been observed in physiological experiments, pharmacological tests, and under clinical conditions; but the site of action where such changes are bound to occur most frequently, the central structures of the autonomic nervous system, has not yet been subjected to a systematic experimental analysis.

It seemed desirable, therefore, to study autonomic reactions in conditions of centrally induced autonomic imbalances. These investigations form the core of this book. From the physiological point of view they appear to be rewarding, since they throw light on the nature and the limits of some of the laws governing the activity of the autonomically innervated organs of the body. To some extent also, the study explains the mechanism underlying the alteration and reversal of autonomic reactions seen in certain clinical conditions.

The procedure, in principle, was this: to alter the reactivity of the autonomic system through a stimulus and to determine this alteration ("tuning") by a test stimulus. In order to analyze such a case, the laws governing summation within the sympathetic and parasympathetic nervous system must be understood. Therefore these laws are discussed first; later they are applied in conditions in which the autonomic centers had been altered ("tuned") reflexly either toward a greater sympathetic or parasympathetic responsiveness (Chapter 1).

This problem was investigated further at the hypothalamic level (Chapter 2). The hypothalamus was selected because of its great significance for the physiology and pathology of the emotions and the adequate separability of parasympathetic and sympathetic functions.* Moreover, the experiments gave an opportunity to investigate the relation between the hypothalamus and the medulla oblongata, and to show that the threshold of important vascular and respiratory reflexes that were thought to act primarily on the medulla is determined by the excitability of the hypothalamus.

States of autonomic imbalance were produced by directly altering the excitability of either the anterior or posterior division of the hypothalamus through physiological or pharmacological means. The responsiveness of the autonomic system to various stimuli was greatly altered, and the laws operating in reflex tuning were found to be valid in states of hypothalamic imbalance. In addition, the investigations led to a result of considerable importance for medicine and neuropsychiatry by showing that certain simple autonomic tests measure semiquantitatively the excitability of the parasympathetic and sympathetic divisions of the hypothalamus in the intact mammalian organism: the effect of mecholyl and other hypotensive drugs on the blood pressure is determined by the excitability of the posterior hypothalamus, whereas the pulse slowing resulting from a given rise of the blood pressure (induced by noradrenaline, for instance) depends on the excitability of the anterior hypothalamus.

The study of sympathetic discharges over a wide range of intensities made it necessary to clarify the relation of the neurogenic to the adrenomedullary discharges (Chapter 3). The experiments showed that the adrenomedullary discharges do not reinforce the sympathetic discharges, as Cannon believed, but inhibit them, and thereby fulfill an important role in homeostasis. Moreover, the ratio of neurogenic to adrenomedullary discharges depends on the excitability of the central nervous system in general, and on that of the hypothalamus in particular. Among the physiological factors which greatly influence hypothalamic excitability and this ratio are the proprioceptive impulses (Chapter 4). This work has important implications for the physiology of different emotional states and for the behavior of the mecholyl test in them.

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* In recent years the important discoveries of Magoun and his school (73, 75, 213, 214, 221–223, 241, 289, 290) have shifted the interest from the hypothalamus to the reticular formation. Both structures have certain functions in common, and the excitability of the posterior hypothalamus seems to depend on the reticular formation (251). Nevertheless, it should not be forgotten that the hypothalamus controls highly integrated actions (151, 153) and is intimately related to the emotions and the endocrine system (94, 141). However, the anatomical and functional connections between the hypothalamus and the reticular formation and the fact that both structures send diffuse impulses to the cortex and receive impulses from the cortex and cerebellum (327) make it very probable that the posterior hypothalamus and the reticular formation undergo similar changes in a variety of conditions.

The influence of the hypothalamus on the viscera is reported in Chapter 5. The main purpose of these experiments is to show the physiological limitations of the tuning of the autonomic nervous system.

Finally, investigations on the influence of hypothalamic imbalance on respiration are reported (Chapter 6). These experiments and the previously described work on the effect of hypothalamic lesions and similar procedures on the blood pressure and heart rate show that the posterior hypothalamus exerts a tonic sympathetic influence on the vascular system and determines the level of respiratory activity.

The work outlined thus far is a study of the influence of reflexly and directly produced central autonomic imbalances on autonomic reflexes and, to use Cannon's terminology, on the sympathetic and parasympathetic "downward" discharge. Fundamental as such work appears to be for physiological and clinical problems, it needs an important complement: the investigation of the "upward"—hypothalamic-cortical—discharge* under the conditions of an altered hypothalamic autonomic balance. The physiological investigations reported in Chapter 7 indicate that changes in hypothalamic excitability and alterations in autonomic balance induced at the diencephalic level have a profound influence on the cortical grey matter. This finding provides the physiological basis for two assumptions: (a) that hypothalamic autonomic disturbances may account for behavior disturbances and (b) that changes in behavior may be paralleled by changes in autonomic tests which indicate hypothalamic reactivity.

This working hypothesis remains to be tested on a large scale. By applying to normal persons and patients the noradrenaline and mecholyl tests indicating the state of the hypothalamus in the intact organism, interesting results have been obtained. It appears that sympathetic reactivity (as measured by the mecholyl test) declines considerably with age. Comparisons between normal and abnormal groups are, therefore, valid only when they are carried out on groups of similar age. Significant differences between the controls and neuropsychiatric patients are reported (Chapter 10). Since certain clinical observations seem to show that the state of hypothalamic excitability and balance varies with the emotional and mental state of the patient, it is suggested that neuropsychiatric therapy should take these factors into consideration. In an attempt to lay some further experimental foundations for these problems, pharmacological experiments are described (Chapter 9) which show the principles through which an altered hypothalamic balance can be changed toward normality.

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* *The expressions "hypothalamic-cortical discharge" and "hypothalamic-cortical system" are chosen for the sake of brevity.* That the cortex has a profound influence on the hypothalamus is discussed in the body of this book. For the specific role which certain cortical areas play in the emotional process, the reader is referred to the work of Bard and Mountcastle (10), Delgado *et al.* (54), Gastaut *et al.* (85), Kaada *et al.* (188), Pribram and Kruger (254), and Schreiner and Kling (271), and to the excellent discussion by Livingston and Worden (215).

The remainder of the monograph is concerned with an evaluation of the significance of this experimental work for the clinical medical sciences and for certain psychological problems.

# *PART I. EXPERIMENTAL INVESTIGATIONS*

Man kann das Zeitalter nicht wählen, in dem man leben und wirken möchte; ich gebrauche meine Tage nach Gelegenheit und Kraft; wie Andere das benutzen werden, was ich darbiete, das fällt ihrem Willen und ihrer Verantwortung anheim. (One may not choose the age in which one would like to live and be productive; my days are employed as occasion and strength permit. How others will use my contributions is subject to their own intentions and sense of responsibility.)

F. Herbart, 1822

Die Hauptsache ist, dass es geschrieben steht; mag nun die Welt damit gebaren, so gut sie kann, und es benutzen, soweit sie fähig ist. (The main thing is that it is written and finished. Let the world take up with it as well as it can and make use of it as far as it is capable.)

Goethe, *Conversations with Eckermann*

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CHAPTER 1

# PHYSIOLOGICAL LAWS CONCERNING AUTONOMIC IMBALANCE

## A. SUMMATION PROCESSES IN THE AUTONOMIC NERVOUS SYSTEM

ALTHOUGH the importance of summation phenomena has been greatly stressed by Sherrington (280) for the somatic nervous system, there exists no systematic work showing their significance for sympathetic and parasympathetic functions although Bronk *et al.* (31, 33) have clearly demonstrated them for autonomic ganglia. For this reason, and as a basis for an understanding of the more complex problems involved in the study of the dynamics of autonomic imbalance, this problem was investigated. Examples will be given showing summation* between (a) two stimuli applied to central autonomic structures (hypothalamus); (b) one central (hypothalamic) stimulus and one peripheral stimulus which elicits an autonomic reflex; (c) two reflex stimuli which elicit autonomic reflexes. This scheme will be followed for the sympathetic and the parasympathetic nervous systems. While most of the experiments illustrate spatial summation, utilizing stimuli overlapping in time and involving different receptors, others concern the effect of temporal summation. In the latter group stimuli were applied at brief intervals, or the duration of a given stimulus was varied and the effect of the increase in duration was investigated.

### 1. Sympathetic Spatial Summation

In the experiments on spatial summation the effect of stimulating two hypothalamic foci singly and in combination was studied on the blood pressure, nictitating membrane, and pulse rate. In most instances the stimuli were near threshold in intensity. In Figure 1 each of the two stimuli which were applied to the left and right hypothalamus respectively caused a slight rise of the blood pressure and no change in the pulse rate.† The left hypothalamic stimulus elicited a

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NOTE. The basis of this chapter is unpublished work with E. S. Redgate.

* These phenomena are analogous to the "immediate spinal induction" which Sherrington (280) studied in spinal reflexes.

† Pulse record is omitted.

contraction of the nictitating membrane, but the right hypothalamic stimulus did not. In combination (Fig. 1*C*) the stimuli produced a significant summation: the contraction of the nictitating membrane was large and a considerable rise of the blood pressure occurred.* It is evident that the effect of the combination of the two stimuli indicates, not an algebraic summation, but rather a potentiation. If suitable stimuli are selected, this potentiation is demonstrable in various forms of spatial summation such as those resulting from stimulation of two hypothalamic stimuli, two sciatic stimuli, or one hypothalamic and one sciatic stimulus. The summation may appear as an increased acceleration of the heart rate, an augmented rise of the blood pressure, or a greater contraction of the nictitating membrane, or as any combination of these phenomena, and it may be demonstrated with subthreshold and suprathreshold stimuli.

## 2. SYMPATHETIC TEMPORAL SUMMATION

The phenomenon of temporal summation so well known from the investigations of the Sherringtonian School on the somatic nervous system is easily demonstrated for the autonomic system. A stimulus applied for 1 second or less may be entirely ineffective on all autonomic indicators used; but if applied for a longer period it will elicit autonomic effects of increasing magnitude. Depending on the site and the parameters of stimulation, the summation or potentiation effect may be greater on one indicator than on another.

Figure 2 shows that with increasing duration of the period of stimulation of the hypothalamus the contraction of the nictitating membrane increases in magnitude and duration. The acceleration of the pulse rate becomes increasingly greater and continues for the duration of the stimulus. Thereafter it is followed by a sudden period of pulse slowing, the significance of which will be discussed on p. 24. The rise

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* In this and all subsequent experiments, the writer convinced himself of the relative constancies of the reactions by repeating the same stimuli. Thus the sympathetic potentiation of the effect on the nictitating membrane illustrated in Figure 1 was demonstrated a second time with a similar series of stimuli not shown in the figure. This series showed likewise that the height of contraction of the nictating membrane was greater under the influence of the combined stimuli than the algebraic sum of the effects of the stimuli applied singly. In numerous figures this constancy of the reaction is illustrated by showing the effect of one of the stimuli before and after the crucial test (see, for instance, Figs. 7*A*, *C*; 8*A*, *C*; 11*A*, *D*; 12*A*, *C*). In others the test involving two stimuli was repeated and shown to be constant (compare Figs. 9*C*, *E*; 10*A*, *D*; etc.). If such constancy could not be obtained, the experiment was rejected. In the writer's opinion, this procedure and the repetition of the experiment in numerous animals ensure results that are independent of individual differences between different animals or gross changes in reactivity which may occur during prolonged experimentation.

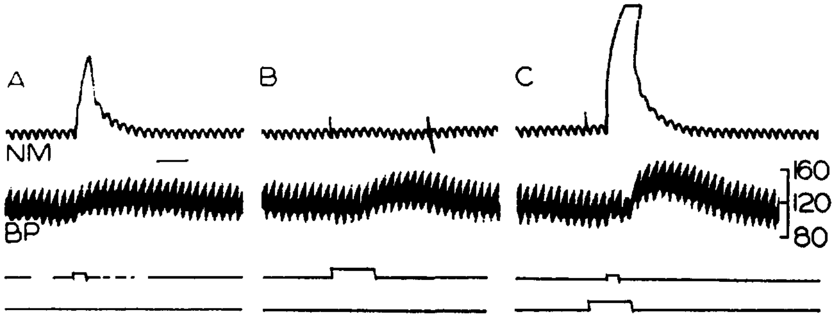

*Figure 1.* Spatial sympathetic summation (*C*) resulting from the stimulation of two hypothalamic sites in the left (*A*) and right (*B*) posterior hypothalamus. The effect on the nictitating membrane is greater than corresponds to an algebraic summation.

Cat, chloralose 85 mg/Kg and urethane 500 mg/Kg. *A*. Left posterior hypothalamic stimulation (S.W.D., 0.8 v., 207 pps, 1.6 ms. for 4 sec.). *B*. Right posterior hypothalamic stimulation (C.D., 1.5 v., 100 pps, 2 ms. for 15 sec.). *C*. Right posterior hypothalamic stimulation as in *B* in combination with left posterior hypothalamic stimulation as in *A* given after 7 sec. of stimulus *B*.

NOTE. All the experiments reported in this book were performed on cats. The reference to the species will therefore be omitted in subsequent legends. The abbreviation S.W.D. stands for *square-wave discharges* throughout the legends. The abbreviation C.D. stands for *condenser discharges*; the duration of these was determined on the basis of a decay of 63 per cent. In the figures the abbreviation NM stands for *nictitating membrane*; NNM, for *normal nictitating membrane*; DNM, for *denervated nictitating membrane*; BP, for *blood pressure*; PR, for *pulse rate*. The pulse rate was recorded with an ordinate writer; a decrease in the amplitude indicates an acceleration of the heart rate. The short horizontal bar denotes the time ( = ten seconds). The injection of drugs is indicated by a short, upward-pointing arrow. The stimulation of peripheral nerves of the central structure is shown by the signal magnet or by horizontal bars.

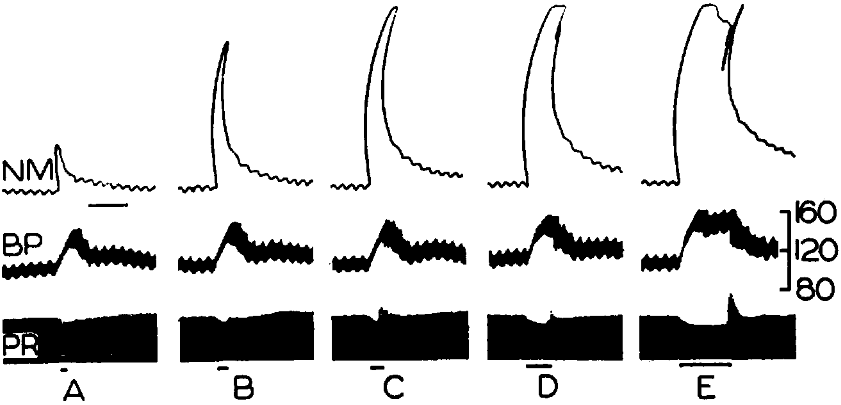

*Figure 2.* Temporal summation resulting from stimulation of a site in the right posterior hypothalamus. Note the progressive increase of sympathetic effects on the nictitating membrane, the blood pressure, and the pulse rate.

Chloralose 75 mg/Kg i.v. *A–E*. Right posterior hypothalamic stimulation (S.W.D., 1 v., 99 pps, 0.8 ms.) for 1, 2, 3, 7, and 15 sec. respectively.

of the blood pressure also increases with increasing duration of the stimulus, but this increase is less marked than in the other sympathetic indicators.

### 3. Parasympathetic Summation

Analogous parasympathetic experiments were performed in which either parasympathetically acting hypothalamic stimuli or sciatic stimuli causing a parasympathetic action were applied singly and in combination. Such experiments show that potentiation occurs also in the parasympathetic system.

Figure 3 illustrates the results of interaction between sciatic and hypothalamic stimuli. *B* and *C* of the figure show the effect of these stimuli when applied singly, *A* when they are administered in combination. It is seen that either stimulus, when applied alone, causes a certain degree of pulse deceleration and a fall of the blood pressure. These effects are, in the case of the sciatic stimulus, more or less confined to the first half of the period of stimulation. Nevertheless, a much greater effect than in the control test *C* is elicited when the hypothalamic stimulus is applied during the second half of the sciatic stimulation period. The abrupt fall of the blood pressure and the greater deceleration of the heart rate during the period of the interaction of the two stimuli (Fig. 3*A*) suggest a potentiation of parasympathetic effects on the blood pressure and pulse rate.

A different type of parasympathetic summation, the interaction between the pulse slowing induced by an injection of noradrenaline (162) and that resulting from hypothalamic stimulation (parasympathetic type), is illustrated in Figure 4. *A* of the figure shows minimal parasympathetic effects on the blood pressure and pulse rate from the hypothalamic stimulus. *B* shows the distinct reflex slowing of the heart rate accompanying the noradrenaline-induced rise of the blood pressure. In the test shown in *C* the injection of noradrenaline follows the onset of the hypothalamic stimulus, but the noradrenaline-induced pressor effect still occurs during the period of hypothalamic stimulation. Under these conditions a parasympathetic summation occurs, since the degree of the slowing of the heart rate is greater in the combination experiments than in those where the hypothalamus was stimulated or noradrenaline was injected separately. Secondly, the greater slowing takes place in spite of the fact that the heightened blood pressure level achieved by the injection of noradrenaline is slightly less in the combination experiment (*C*) than in the corresponding control test (*B*).

Temporal facilitation can be demonstrated also for the parasym-

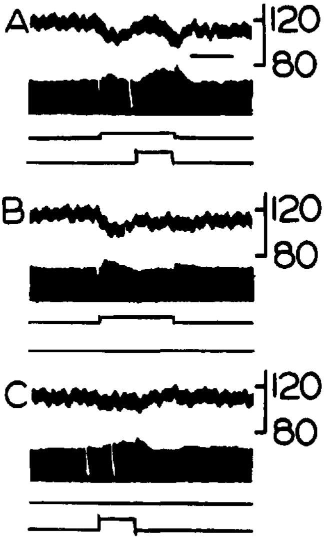

*Figure 3.* Parasympathetic summation resulting from the interaction of a parasympathetically acting hypothalamic stimulus (*A* and *C*) with a stimulation of the sciatic nerve (*B*) with a similar parasympathetic action. The summation appears as a greater fall of the blood pressure and a more marked pulse slowing during the interaction of the two stimuli than corresponds to an algebraic summation.

Chloralose 50 mg/Kg and urethane 400 mg/Kg. *A*. Sciatic stimulation (S.W.D., 2 v., 38 pps, 3.2 ms., for 20 sec.) in combination with left posterior hypothalamic stimulation (C.D., 3.3 v., 100 pps, 3 ms. for 10 sec.) after 10 seconds. *B*. Sciatic stimulation as in *A* by itself. *C*. Left posterior hypothalamic stimulation as in *A*, by itself.

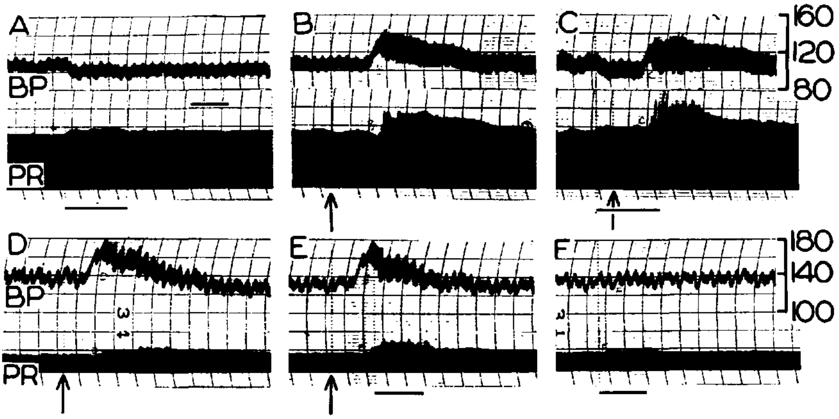

*Figure 4.* Parasympathetic summation resulting from the interaction of hypothalamic stimulation and the injection of noradrenaline (indicated by the arrows). The summation appears as a greater slowing of the pulse rate (i.e., a greater increase in the amplitude in the pulse rate record) in *C* and *E* than in the corresponding control experiments.

The upper figure is taken from an experiment on a cat anesthetized with chloralose 75 mg/Kg i.v. The lower figure is from another animal anesthetized with chloralose 50 mg/Kg and urethane 400 mg/Kg. *A*. Right posterior hypothalamic stimulation (S.W.D., 1.5 v., 99 pps, 0.4 ms. for 20 sec.). *B*. 2 gammas of noradrenaline i.v. *C*. Right posterior hypothalamic stimulation as in *A* in combination with 2 gammas of noradrenaline injected intravenously after 5 seconds of stimulation. *D*. 1 gamma of noradrenaline i.v. *E*. 1 gamma of noradrenaline i.v. in combination with left posterior hypothalamic stimulation (S.W.D., 1.5 v., 51 pps. 1.6 ms., for 15 sec.) at the blood pressure maximum. *F*. Left posterior hypothalamic stimulation as in *E*, by itself.

pathetic system. Stimuli which on excitation of the hypothalamus or the central end of the sciatic nerve elicit a parasympathetic response (fall of the blood pressure and slowing of the heart rate) evoke these effects in an increasing degree as the duration of the stimulus is increased. Moreover, temporal facilitation of parasympathetic effects may be shown by applying the same stimulus repeatedly at a constant interval. Under these conditions the blood pressure falls progressively to lower levels.

The experiments show that the interaction of two sympathetic as well as the interaction of two parasympathetic stimuli greatly increases sympathetic and parasympathetic effects respectively. The result of this interaction is greater than can be accounted for by algebraic summation of the effector responses.

## B. STUDIES ON THE REACTIVITY OF THE AUTONOMIC NERVOUS SYSTEM IN REFLEXLY INDUCED STATES OF IMBALANCE *

The experiments presented in the preceding pages have shown the effectiveness of summation processes for each of the two divisions of the autonomic nervous system. This work was supplemented by studies (to be described in this and later sections) in which the summation processes were investigated through the use of stronger (suprathreshold) stimuli, which change the balance of the autonomic system. For the sake of describing and understanding these experiments on autonomic imbalance, it is essential at this point to introduce the concept of "tuning."

Under strictly physiological conditions the responsiveness of the autonomic nervous system in its central structures as well as in its peripheral parts is, other conditions being equal, determined by the state of excitability and rate of discharge of the sympathetic and parasympathetic "centers," and it is generally assumed that the two autonomic divisions are in a state of balance. Now it is possible to alter this state fundamentally by inducing a relatively strong sympathetic or parasympathetic reflex or by changing the excitability and rate of discharge of the autonomic centers. The second of these possibilities was investigated in the experiments to be described in Chapter 2. In these experiments, either by stimulation, injection, or coagulation, the the excitability and rate of central discharge were altered in one autonomic division. This change must have led secondarily to a disturbance of the autonomic balance.

At present we are concerned with those states of autonomic imbalance that can be produced reflexly. These states are best achieved

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* Unpublished work with E. S. Redgate.

through sino-aortic reflexes. Any procedure that will produce a rise of the blood pressure (and, consequently, of the pressure in the sino-aortic area) will lead to increased parasympathetic and reciprocally lessened sympathetic discharges, whereas an experimentally induced fall of the blood pressure causes increased sympathetic and reciprocally lessened parasympathetic discharges. The fall of the blood pressure and the reduction of the heart rate following an increase in the pressure of the carotid sinus and, conversely, the rise of the blood pressure and the acceleration of the pulse rate following a fall of the pressure in the carotid sinus, are familiar examples of sino-aortic reflexes on the autonomic nervous system. By testing the effect of parasympathetic stimuli when the blood pressure has been raised, we may study parasympathetic summation processes; similarly, by testing the action of sympathetic stimuli when the blood pressure has been lowered reflexly, we may study sympathetic summation processes. To express this matter somewhat differently, these studies will give us an opportunity to investigate the influence of parasympathetic or sympathetic tuning (i.e., the state of autonomic imbalance induced by a reflexly augmented parasympathetic or sympathetic rate of discharge) on the responsiveness of the autonomic system. At present the discussion will be restricted to the action of sympathetic stimuli during sympathetic reflex tuning and to the action of parasympathetic stimuli during parasympathetic reflex tuning. Later on, mixed effects, such as the action of sympathetic stimuli during parasympathetic tuning, will be considered.

### 1. THE ACTION OF SYMPATHETIC STIMULI DURING SYMPATHETIC REFLEX TUNING

Instead of inducing a state of sympathetic tuning by lowering the pressure in the surgically isolated and perfused carotid sinus, in our experiment the blood pressure was altered by means of intravenously injected drugs. For sympathetic tuning induced by hypotension acetylcholine, mecholyl, and histamine were used.

Figure 5 shows the effect on the nictitating membrane, blood pressure, and pulse rate of (*A*) 3.75 gammas of acetylcholine; (*B*) hypothalamic stimulation; and (*C*) the two in combination. The hypothalamic stimulus was near the threshold, since the action on the blood pressure was very slight and the effect on the nictitating membrane moderate in degree. When this stimulus was given during acetylcholine hypotension, as the blood pressure began to return to the control level (Fig. 5*C*) three changes were noted: (a) the contraction of the nictitating membrane was increased and occurred more rapidly; (b) the blood

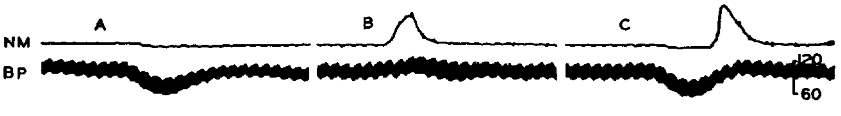

*Figure 5.* Increased sympathetic responsiveness, indicated by the contraction of the nictitating membrane, to hypothalamic stimulation during acetylcholine-induced hypotension (injection indicated by the arrow).

Pentothal anesthesia. *A*. 3.75 gammas of acetylcholine i.v. *B*. Bipolar stimulation of the posterior hypothalamus. *C*. Combination of the two stimuli (the hypothalamic stimulus is given as the blood pressure begins to rise).

pressure returned more quickly than in the control experiment (Fig. 5*A*) and even overshot slightly; (c) the pulse rate was increased more than the increase noted in *A* and *B* of the experiment.* These changes show the greater effectiveness of the hypothalamic stimulus during the acetylcholine-induced hypotension than under control conditions. Bearing in mind that the effect of the hypothalamic stimulus on the blood pressure and heart rate is minimal under control conditions and that acetylcholine alone does not elicit a contraction of the nictitating membrane in this experiment, it follows that Figure 5 illustrates a sympathetic *potentiation* under conditions of reflex sympathetic tuning.

In view of the importance of this finding, a similar experiment (Fig. 6) may be discussed. In this case the hypothalamic stimulus was of suprathreshold intensity, as indicated by the marked rise of the blood pressure, the acceleration of the pulse rate, and the moderate contraction of the nictitating membrane shown in Figure 6*B*. Acetylcholine alone caused neither a change in the pulse rate nor a contraction of the nictitating membrane. On application of the hypothalamic stimulus in the acetylcholine-induced state of hypotension, the contraction of the nictitating membrane was greatly increased and the pulse acceleration was increased in duration. Similar results were obtained in experiments involving the interaction between a mecholyl-induced hypotension and hypothalamic stimulation.

Finally, an experiment, illustrated in Figure 7, was performed to demonstrate the effect of sympathetic reflex tuning by histamine hypotension. Histamine by itself, as shown in *D* of the figure, caused an acceleration of the pulse and a slow contraction of the nictitating membrane.† When during the phase of recovery of the blood pressure

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* This effect is not very clear in the figure on account of the reduction in size.

† This and similar experiments suggest that the sympathetic discharge induced by hypotension starts approximately when the hypotensive effect is maximal. For this reason the hypothalamic stimulus was always applied in these experiments as the blood pressure recovered and not during the initial fall.

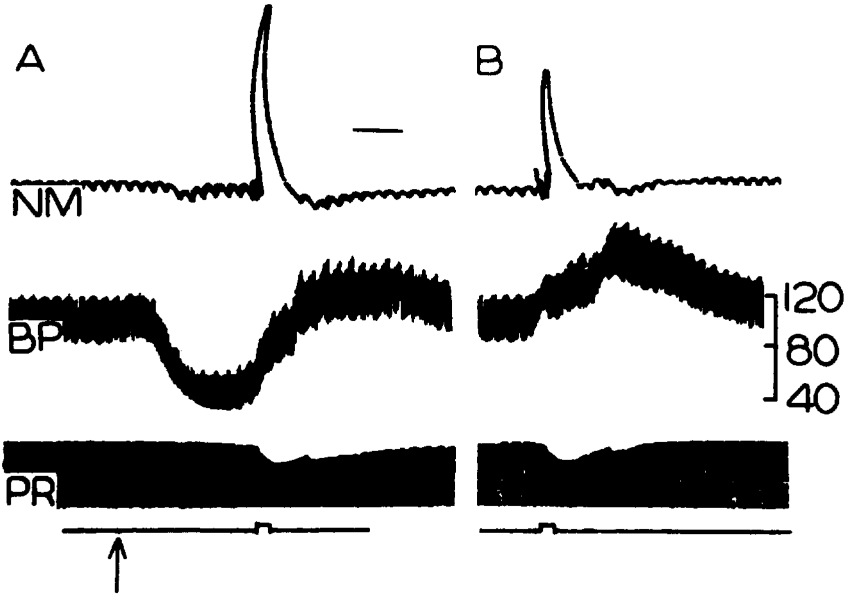

*Figure 6.* Increased hypothalamic responsiveness (nictitating membrane) during acetylcholine-induced hypotension (injection indicated by the arrow).

Chloralose 85 mg/Kg and urethane 200 mg/Kg. *A*.10 gammas of acetylcholine i.v. in combination with left posterior hypothalamic stimulation (S.W.D., 1.5 v., 99 pps, 0.4 ms. for 3 sec.) at blood pressure minimum. *B*. Left posterior hypothalamic stimulation as in *A*, by itself

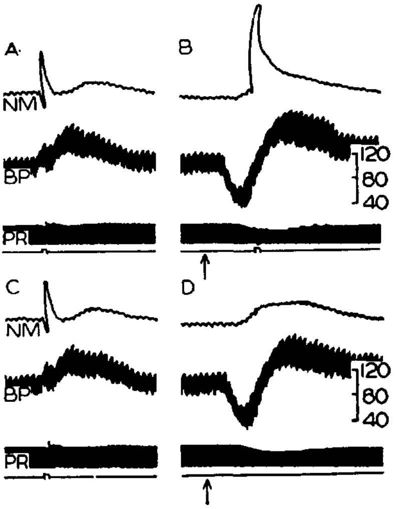

*Figure 7.* Increased hypothalamic responsiveness shown by the contraction of the nictitating membrane during histamine-induced hypotension (injections indicated by the arrows). Note the reversibility of this phenomenon.

Chloralose 85 mg/Kg i.v. *A*. Left posterior hypothalamic stimulation (S.W.D., 2 v. 99 pps, 1.6 ms. for 2 sec.). *B*. 10 gammas of histamine i.v. in combination with left posterior hypothalamic stimulation during recovery of the blood pressure. *C*. Same as *A*. *D*. 10 gammas of histamine i.v.

the hypothalamic stimulus was applied, it resulted in a much greater contraction of the nictitating membrance (Fig. 7*B*), superimposed on the slow contraction caused by the histamine hypotension. This effect, again, is clearly a case of sympathetic potentiation.

On the basis of these experiments it may be said that *in the normal animal hypotensive drugs such as acetylcholine, mecholyl, and histamine evoke a state of sympathetic tuning during which a central sympathetic stimulus (applied to the hypothalamus, for instance) is much more effective than under control conditions.*

### 2. THE ACTION OF PARASYMPATHETIC STIMULI DURING PARASYMPATHETIC REFLEX TUNING

For the purpose of demonstrating parasympathetic reflex tuning, the blood pressure was raised by the injection of noradrenaline. At the height of the blood pressure response a hypothalamic stimulus producing largely parasympathetic effects was applied and its action was compared with that seen when the blood pressure was at its control level. Such a stimulus, as shown in Figure 4*F*, produced no change in the blood pressure, but slightly slowed the heart rate. A similar degree of slowing was produced by the injection of noradrenaline (Fig. 4*D*), but a much greater slowing occurred when the hypothalamic stimulus was applied during the noradrenaline-induced hypertension. The experiment shows clearly that the resulting parasympathetic effect is greater than the algebraic sum of the two individual effects.*

That parasympathetic tuning may lead to potentiation can also be demonstrated by using a parasympathetically acting stimulation of the sciatic nerve as a test stimulus. Such a stimulus, as shown in Figure 8*D*, caused only a very slight fall of the blood pressure and no change in the heart rate. When this stimulus was applied at the height of the adrenaline-induced pressor effect (Fig. 8*A*, *C*), an abrupt and marked fall of the blood pressure ensued. This fall was associated with a greater slowing of the heart rate than occurred during the noradrenaline test (*B*). The reversibility of this dramatic effect of parasympathetic tuning and potentiation of two parasympathetic reflex stimuli is well illustrated in this figure.

Parasympathetic tuning, although ordinarily of a lesser degree, is observable also when a parasympathetic stimulus is applied during the slight overshooting of the blood pressure which occurs following the hypotensive action of acetylcholine and particularly of histamine. The parasympathetically acting hypothalamic stimulus used in the ex-

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* In spite of the fact that the pressor effect is maintained less in *E* than in *D*!

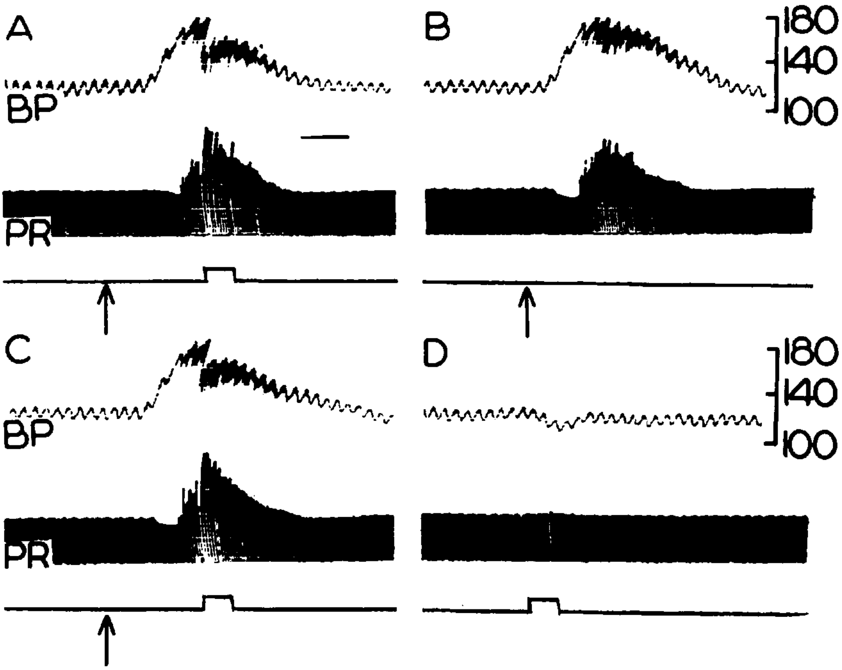

*Figure 8.* The effect of sciatic stimulation (parasympathetic type) during noradrenaline-induced tuning (injections indicated by the arrows). Note the increased slowing of the pulse rate and the abrupt fall of the blood pressure in response to sciatic stimulation in *A* and *C*.

Chloralose 80 mg/Kg i.v. *A*. 0.5 gammas of noradrenaline i.v. in combination with sciatic stimulation (C.D., 5.5 v., 38 pps, 2 ms. for 7 sec.) at blood pressure maximum. The horizontal bar below the blood pressure curve indicates 10 seconds. *B*. 0.5 gammas of noradrenaline i.v. *C*. Same as *A*. *D*. Sciatic stimulation as in *A*, by itself.

periment shown in Figure 9 was nearly subthreshold, since it elicited only a trace of a depressor action at the beginning of the stimulation and a temporary slight deceleration of the pulse rate (*F*). Histamine (*B*) and acetylcholine (*D*) by themselves elicited a pulse acceleration during most of the time of the hypotensive action. Later, as the blood pressure increased slightly above the control level, there occurred not only a return of the heart rate to the control level but also an additional minimal slowing. As the hypothalamic stimulus was applied in the post-hypotensive phase, this slowing was increased in magnitude and duration while the overshooting of the blood pressure was lessened or abolished (Fig. 9*A*, *C*, *E*).

These changes may appear to be slight. But the fact that they occur regularly and can be repeated several times in the same preparation

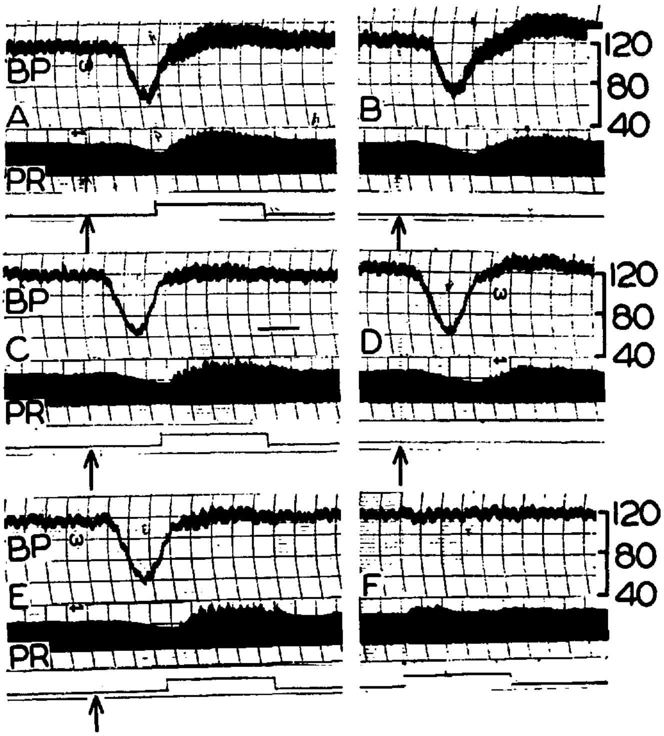

*Figure 9.* The effect of a hypothalamic stimulus (parasympathetic type) during histamine- and acetylcholine-induced rises of the blood pressure (injections indicated by the arrows). The pulse rate is slowed more than in the control tests.

Chloralose 50 mg/Kg and urethane 400 mg/Kg. *A.* 12.5 gammas of histamine i.v. in combination with left posterior hypothalamic stimulation as in *F. B.* 12.5 gammas of histamine i.v. *C.* 10 gammas of acetylcholine i.v. in combination with left posterior hypothalamic stimulation as in *F. D.* 10 gammas of acetylcholine i.v. *E.* 10 gammas of acetylcholine i.v. in combination with left posterior hypothalamic stimulation as in *F.* *F.* Left posterior hypothalamic stimulation as in *A, C,* and *E,* by itself.

gives weight to our interpretation. Moreover, it should be borne in mind that the increased slowing of the pulse rate occurs here in spite of the fact that, as already mentioned, the changes in the blood pressure oppose reflex slowing. It may therefore be concluded that the reflex tuning of the parasympathetic system brought about noradrenaline-induced hypertension or occurring during the slight hypertensive phase succeeding an acetylcholine- or histamine-induced hypotension leads to an increase in the effectiveness of parasympathetically acting stimuli regardless of whether they act on central autonomic structures directly or reflexly.

## 3. AUTONOMIC TUNING AND RECIPROCAL INNERVATION

In view of the fact that reflexes of the autonomic nervous system lead generally to an excitation of the sympathetic division and to an inhibition of the parasympathetic division or vice versa, it seemed of interest to investigate this phenomenon of reciprocal innervation under conditions of autonomic tuning. In the preceding pages the effect of sympathetic (or parasympathetic) tuning on the responsiveness of the autonomic system to sympathetic (or parasympathetic) stimuli has been described; it is now our task to determine the responsiveness of the parasympathetic system under conditions of experimentally induced sympathetic dominance* or tuning and vice versa.

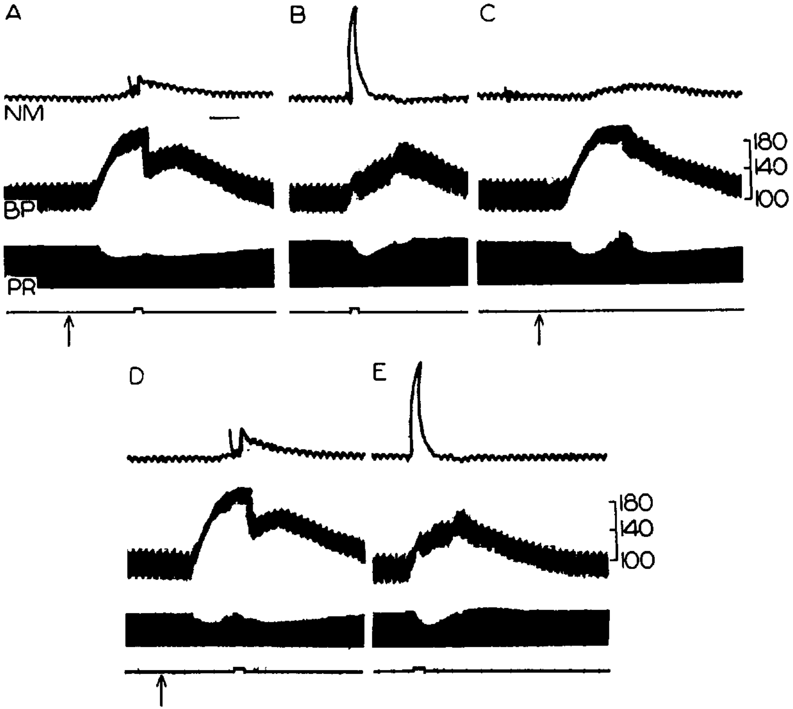

*Figure 10.* The action of a sympathetic hypothalamic stimulus during noradrenaline-induced tuning. Note the reduction in the size of the contraction of the nictitating membrane and the reversal of the blood pressure effect.

Chloralose 85 mg/Kg and urethane 200 mg/Kg. *A*. 2 gammas of noradrenaline i.v. in combination with left posterior hypothalamic stimulation (S.W.D., 1.5 v., 99 pps, 0.4 ms. for 3 sec.). *B*. Left posterior hypothalamic stimulation (S.W.D., 1.5 v., 99 pps, 0.4 ms. for 3 sec.). *C*. 2 gammas of noradrenaline i.v. *D*. 2 gammas of noradrenaline i.v. in combination with hypothalamic stimulation (sympathetic type), (1.8 v., 74 pps, 0.8 ms. for 4 sec.). *E*. Hypothalamic stimulation as in *D*, by itself.

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* The imbalance of the autonomic centers which is induced by reflex "tuning" leads to an increased excitability of one division of the autonomic system and to the inhibi-

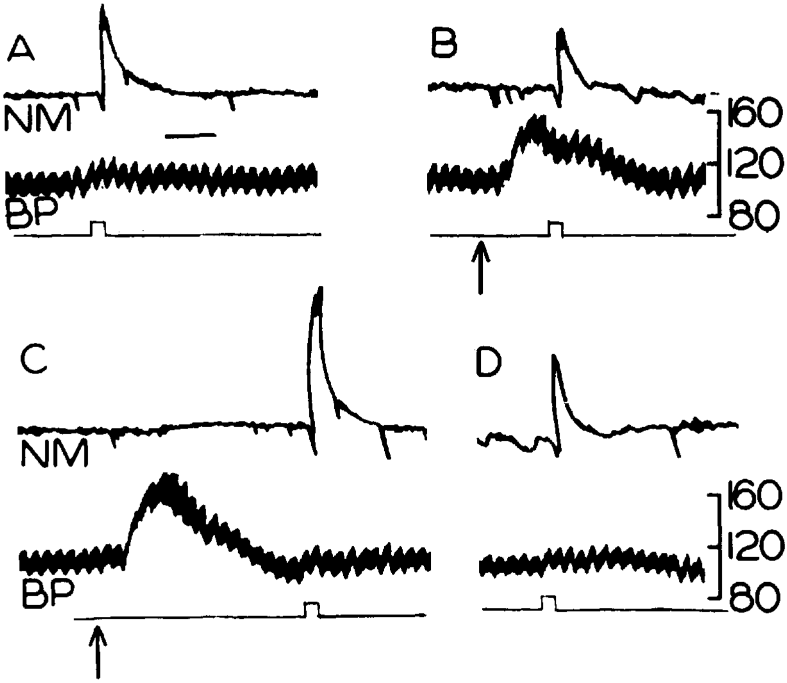

*Figure 11.* Responsiveness to hypothalamic stimulation during a noradenaline-induced rise of the blood pressure (injection indicated by the arrows) and also during a subsequent hypotensive phase. Note that the contraction of the nictitating membrane is decreased in *B* and increased in *C*.

Chloralose 65 mg/Kg and urethane 400 mg/Kg i.v. *A*. Left posterior hypothalamic stimulation (C.D., 100 pps, 2 ms. for 3 sec.). *B*. 1 gamma of noradrenaline i.v. in combination with left posterior hypothalamic stimulation at blood pressure maximum. *C*. 2 gammas of noradrenaline i.v. in combination with left posterior hypothalamic stimulation at "undershooting" of the blood pressure. *D*. Same as *A*.

### a. PARASYMPATHETIC TUNING AND SYMPATHETIC REACTIVITY

Under conditions of noradrenaline-induced parasympathetic tuning, illustrated in Figures 10 and 11*B*, sympathetic reactivity is greatly and reversibly diminished, as the records of the nictitating membrane clearly show. Figure 10 shows, in addition, that the acceleration of the pulse rate which occurs during and after the period of hypothalamic stimulation in the control (*B*) does not occur when the stimulus is applied to an animal in a state of noradrenaline-induced hypertension (*A*). Since the pressor effect of hypothalamic stimulation is likewise

tion of the other, as the following experiments will show. One may, therefore, speak of a shift in dominance as the result of "tuning." The "dominant" autonomic division is characterized by its greater responsiveness to direct or reflex excitation.

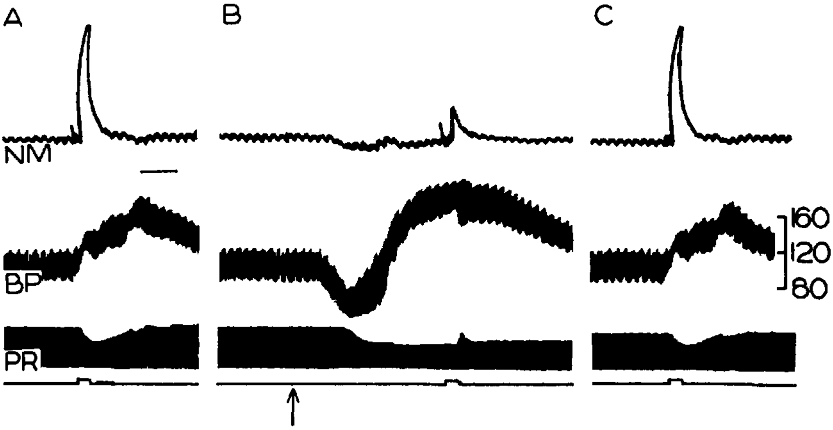

*Figure 12.* Hypothalamic effects during a histamine-induced hypertensive phase (injection indicated by the arrow). Note that the contraction of the nictitating membrane is diminished and that parasympathetic reactions prevail on cessation of the hypothalamic stimulus.

Chloralose 85 mg/Kg and urethane 200 mg/Kg. *A*. Right posterior hypothalamic stimulation (S.W.D., 1.8 v., 74 pps, 0.4 ms. for 4 sec.). *B*. 10 gammas of histamine i.v. with right posterior hypothalamic stimulation as in *A*. *C*. Right posterior hypothalamic stimulation as in *A*.

eliminated,* three criteria (blood pressure, pulse rate, and contraction of the nictitating membrane) bring us to the conclusion that *during the noradrenaline-induced parasympathetic tuning the responsiveness of the sympathetic system is greatly diminished.*

That this effect occurs also in other forms of parasympathetic tuning is shown in Figure 12. During histamine-induced overshooting of the blood pressure, the sympathetic responsiveness is reduced, as indicated by the nictitating membrane (*B*). This experiment shows likewise that the rise of the blood pressure and the acceleration of the pulse rate which accompany hypothalamic stimulation under control conditions (*A* and *C*) are absent during histamine-induced parasympathetic tuning.

### b. SYMPATHETIC TUNING AND PARASYMPATHETIC REACTIVITY

It was originally planned to investigate the problem of parasympathetic reactivity in states of sympathetic tuning by producing such states through the injection of hypotensive drugs and then testing the noradrenaline-induced reflex slowing of the heart. However, since the slowing of the heart rate by noradrenaline depends greatly on the absolute blood pressure level, this experiment had to be abandoned.* In its stead a state of sympathetic tuning was induced by sciatic or hypothalamic stimulation, which involved only a slight change in the blood pressure. During such a state of sympathetic tuning, noradrenaline was injected (Fig. 13); the lessening of the parasympathetic reflex effects is indicated by the fact that the latent period of the slowing of the heart rate was greater in this state (*B*) than in the control situation (*C*).

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* The fall of the blood pressure after the stimulation will be discussed on p. 30.

Even more striking results, as illustrated in Figure 14, were obtained when stimulation of the sciatic nerve was used for sympathetic tuning. Here again the sympathetic tuning reduced the parasympathetic reflex effects resulting from noradrenaline-induced hypertension, in spite of the fact that the pressor effect was much greater under the conditions represented in *A* than under those in *B*. It is worthy of note that tuning may greatly alter the responsiveness of the heart rate, although the tuning stimulus alone causes no alteration (Fig. 13*A*) or only a minimal alteration in the heart rate (Fig. 14*C*).

From these experiments it may be concluded that *sympathetic tuning is accompanied by a lessened responsiveness to parasympathetic reflex stimuli.* Since a corresponding statement, as we have seen, applies to the parasympathetic tuning, it follows that *the law of reciprocal innervation remains valid for states of an induced autonomic imbalance.*

### C. TUNING AND SUCCESSIVE INDUCTION

In preparations in which both branches of the autonomic nervous system show a high degree of reflex excitability, it has frequently been seen that a hypothalamic stimulus elicits sympathetic signs *during* the stimulation, but parasympathetic effects immediately after the stimulation ceases. Whereas the rise of the blood pressure is associated with an acceleration of the pulse *during the stimulation*, after the stimulation the heart rate abruptly slows. At first, after the cessation of the stimulus, the blood pressure is still above the control level but then it falls gradually or abruptly. We propose for this phenomenon the term "successive autonomic induction."† Other conditions being equal, the successive autonomic induction increases with the effectiveness of the sympathetic stimulation, whether the increased effectiveness is due to an increase in the intensity, the frequency, or

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* There was no pulse-slowing reflex at the low blood pressure after the injection of hypotensive drugs.

† This phenomenon is analogous to Sherrington's "successive spinal induction," according to which "by virtue of . . . spinal contrast . . . the extension-reflex predisposes to and may actually induce a flexion reflex" and vice versa.

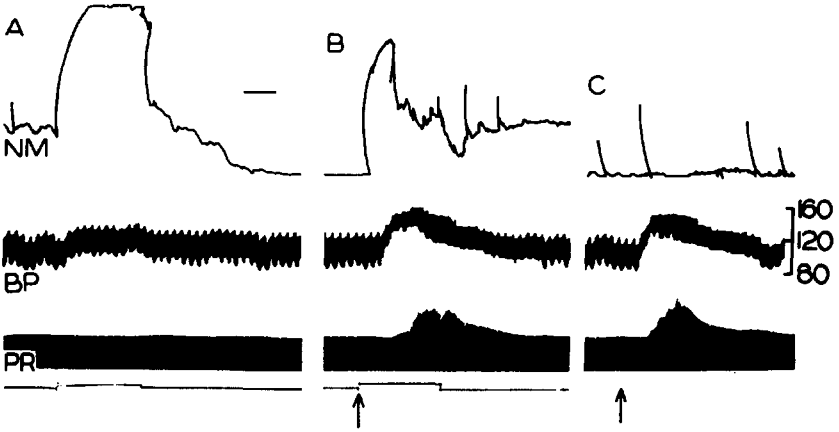

*Figure 13.* The interaction of hypothalamic stimulation and noradrenaline (injected at the arrows). Note that the duration of the contraction of the normal nictitating membrane is shortened and that the noradrenaline-induced slowing of the pulse rate is delayed (in *B*).

Chloralose 65 mg/Kg i.v. *A*. Left posterior hypothalamic stimulation (S.W.D., 1.0 v., 99 pps, 0.8 ms. for 30 sec.). *B*. Left posterior hypothalamic stimulation as in *A* in combination with the injection of 2 gammas of noradrenaline i.v. *C*. 2 gammas of noradrenaline i.v.

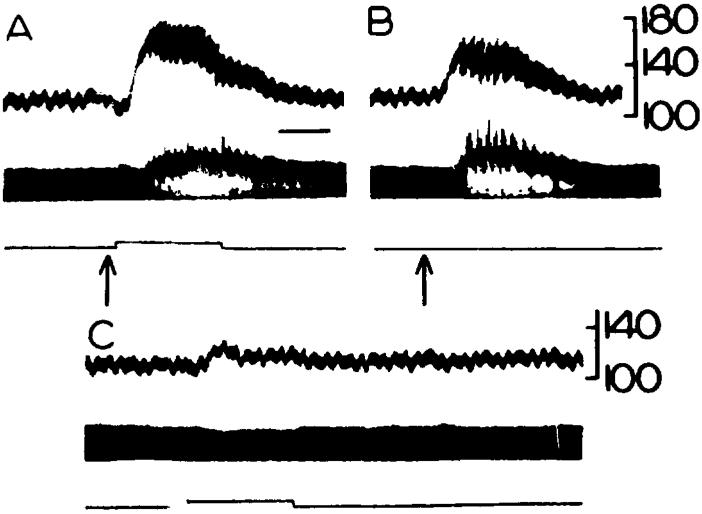

*Figure 14.* The effect of sympathetic tuning induced by stimulation of the sciatic nerve on the reflex slowing following the injection of noradrenaline (indicated by the arrows). Note the lesser slowing of the heart rate in *A* in spite of the greater blood pressure rise than in *B*.

Chloralose 50 mg/Kg and urethane 400 mg/Kg. *A*. Sciatic stimulation (S.W.D., 2 v., 38 pps, 3.2 ms. for 20 sec.), in combination with 1 gamma of noradrenaline i.v. *B*. 2 gammas of noradrenaline i.v. by itself. *C*. Sciatic stimulation as in *A*, by itself.

the duration of the stimulus (Fig. 2) or to an increase in the duration of the individual square waves which compose it.

*(1) Parasympathetic tuning and successive induction.* From this description it is evident that we are dealing here with an indirect parasympathetic phenomenon which depends on the intensity of the preceding sympathetic excitation. But this phenomenon also depends on the tuning of the autonomic nervous system. If the hypothalamic stimulus is applied during a noradrenaline hypertension (i.e., in a state of parasympathetic tuning) the successive autonomic induction is greatly increased. Thus the poststimulatory pulse slowing is much greater during the noradrenaline test (Fig. 15*B*) than under the control conditions (Fig. 15*A*).

Figure 12 shows the influence of a histamine-induced hypertension on successive autonomic induction. In this experiment a hypothalamic stimulus was applied which resulted in a strong sympathetic effect on all indicators (nictitating membrane, blood pressure, and pulse rate) under control conditions (*A* and *C*). There was a marked acceleration of the heart rate, which persisted for a considerable time after the cessation of the stimulus. During the histamine test the pulse rate was greatly accelerated, and this change persisted during the sub-

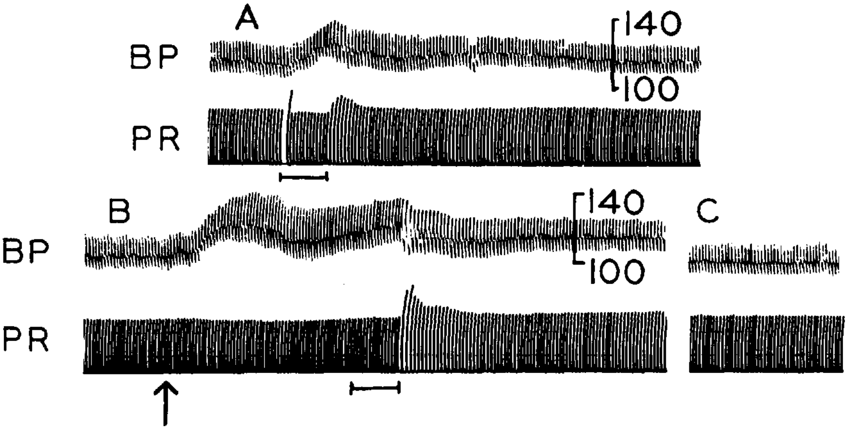

*Figure 15.* The effect of stimulation of the anterior hypothalamus during noradrenaline-induced hypertension (injection indicated by the arrow). Note the increased slowing of the heart rate (in *B*).

*A.* Hypothalamic stimulation (S.W.D., 1.5 v., 51 pps, 1.6 ms. for 5 sec.). *B.* This same stimulus during a rise of the blood pressure induced by 10 gammas of noradrenaline i.v. *C.* Blood pressure and pulse rate 50 seconds after the end of *B.* Bipolar hypothalamic stimulation. (Anterior electrode localized 1 mm. dorsal to posterior border of optic chiasma, 3 mm. lateral; posterior electrode in infundibular hypothalamus 1 mm. anterior to mammillary bodies.)

sequent hypertension. As the hypothalamic stimulus was applied during this phase, it failed to augment the increase in the pulse rate, but immediately following the stimulation period it elicited a distinct slowing which was absent in the control tests (*A* and *C*). The experiment shows that parasympathetic tuning (histamine- or noradrenaline-induced hypertension) greatly increases the tendency to successive autonomic induction. This result provides another, more indirect, illustration of the principle that parasympathetic summation (potentiation) processes are facilitated during parasympathetic tuning.

A quantitative comparison between these two types of parasympathetic tuning may be made by studying Figure 16, which illustrates the effects of noradrenaline- and histamine-induced hypertension on successive induction in the same animal. The degree of hypertension is similar in both tests, but the responsiveness to successive induction

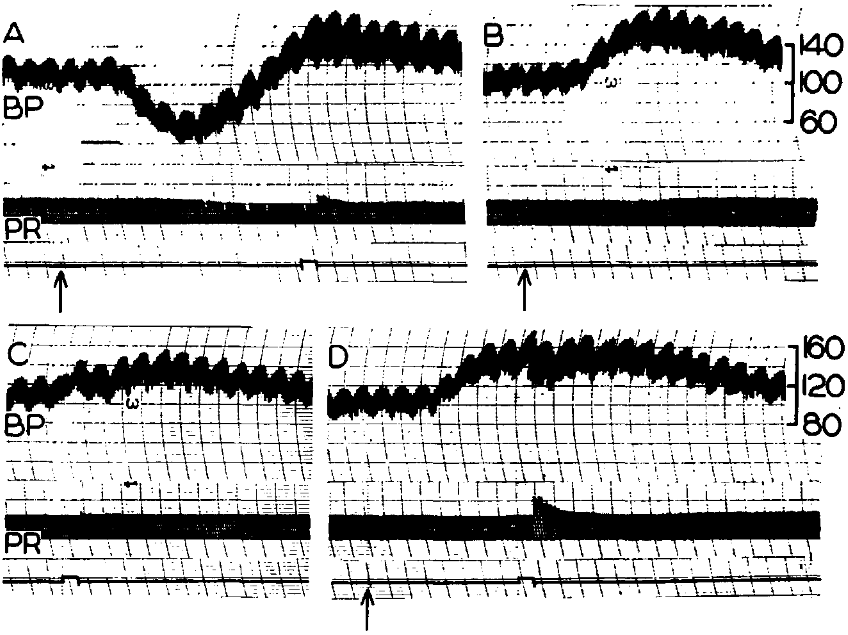

*Figure 16.* Parasympathetic induction under conditions of histamine- and noradrenaline-induced hypertension (injection indicated by the arrows). Note the increased parasympathetic effects (slowing of the pulse rate) following the hypothalamic stimulation (in *A* and *D*).

Chloralose 85 mg/Kg. *A*. 10 gammas of histamine i.v. in combination with left posterior hypothalamic stimulation (S.W.D., 2 v., 99 pps, 1.6 ms. for 2 sec.). *B*. 2 gammas of noradrenaline i.v. *C*. Left posterior hypothalamic stimulation by itself. *D*. 2 gammas of noradrenaline i.v. in combination with left posterior hypothalamic stimulation.

is quite different. The hypothalamic stimulus, which causes only a trace of a successive induction in the control test (*C*), produces, during the histamine hypertension (*A*) a moderate, and during the noradrenaline test (*D*) a considerable, degree of successive induction. The following interpretation of this quantitative difference is suggested. Noradrenaline induces a state of pure parasympathetic tuning, indicated in Figure 16*B* by the gradual, slight deceleration of the pulse rate. Histamine hypertension, however, occurs while the sympathetic discharges induced by the hypotensive action of histamine still continue, as indicated by the persistence of the increased pulse rate shown in Figure 16*A*. Therefore in this case the parasympathetic tuning resulting from the overshooting of the blood pressure is partially opposed by a sympathetic discharge. This opposition accounts for a lesser parasympathetic effect under conditions which are productive of successive autonomic induction than is seen under the otherwise similar conditions of the test shown in Figure 16*D*, in which these opposing discharges are absent.

*(2) Sympathetic tuning and successive induction.* As was to be expected, the opposite effect, i.e., an inhibition of the parasympathetic phase of the successive induction phenomenon, takes place under conditions of sympathetic tuning. Experiments producing sympathetic tuning through hypotension may illustrate the results.

*A* and *C* of Figure 17 show respectively the effects of hypothalamic stimulation and of acetylcholine; *B* shows their combined effect when the hypothalamic stimulation is applied as the blood pressure begins to recover from the acetylcholine-induced hypotension. In the experiment shown in *A* the hypothalamic stimulus did not change the pulse rate significantly during stimulation, but after stimulation the rate decreased. This phenomenon was minimal during the experiment with sympathetic tuning shown in *B*.

A similar effect of sympathetic tuning induced by histamine is shown in Figure 7. In the control experiments (*A*, *C*) a brief parasympathetic discharge occurred each time at the end of the hypothalamic stimulation period; but this effect was absent during the marked sympathetic tuning, induced by histamine hypotension, which produced a considerable pulse acceleration.

The two experiments illustrate the fact that sympathetic tuning, regardless of whether it leads to overt sympathetic discharges on the pulse rate (as in Fig. 7*D*) or not (as in Fig. 17*C*), reduces the poststimulatory successive (parasympathetic) induction.

Taken together with the data presented in the preceding section, it may be stated that the rules of autonomic tuning apply to the phe-

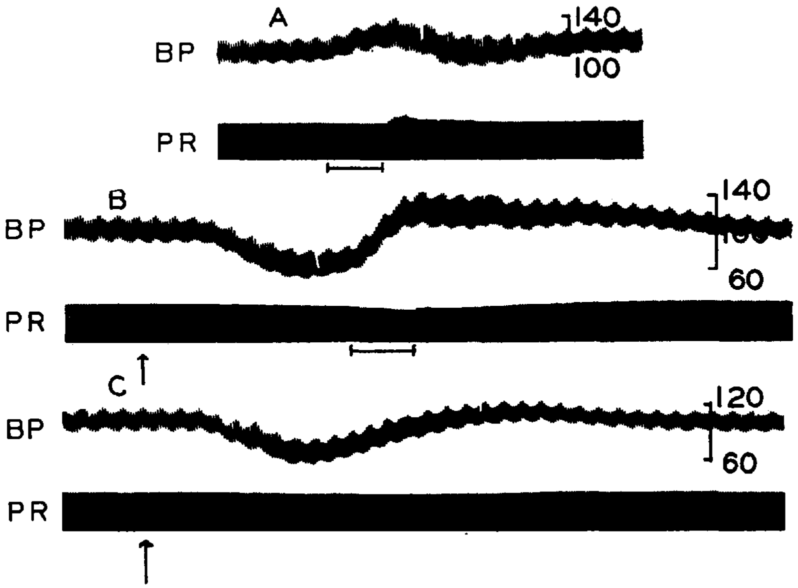

*Figure 17.* The effect of anterior hypothalamic stimulation during acetylcholine-induced hypotension (injection indicated by the arrows). Note the absence of the poststimulatory slowing of the heart rate (in *B*).

*A*. Hypothalamic stimulation (S.W.D., 2 v., 45 pps, 0.8 ms. for 10 sec.). *B*. 5 gammas of acetylcholine i.v. in combination with hypothalamic stimulation as in *A*. *C*. 5 gammas of acetylcholine i.v., by itself.

nomenon of successive autonomic induction. A state of sympathetic tuning tends to diminish the successive parasympathetic induction, whereas a state of parasympathetic tuning tends to intensify the induction. This statement applies to various procedures of tuning. Thus the sympathetic tuning during the recovery of the blood pressure from drug-induced hypotension or the sympathetic tuning during a brief period of asphyxia reduces the parasympathetic induction in a similar manner. Obviously processes of summation and potentiation, as shown earlier, are involved. Some emphasis on this phenomenon is necessary because it shows that the fundamental alterations in the reactivity of the autonomic nervous system in conditions of sympathetic or parasympathetic tuning modify not only the direct effect of stimuli acting on this system but also their after-effects. Of course, the reason for this is that the action of a stimulus as well as its after-effect is determined by the autonomic balance between sympathetic and parasympathetic processes, and it is this balance that is disturbed by autonomic tuning.

## 4. REVERSAL OF AUTONOMIC EFFECTS AS THE RESULT OF TUNING

It was observed by Darrow and Gellhorn (52) that during an adrenaline-induced rise of the blood pressure, sympathetic effects resulting either from stimulation of the central end of a peripheral nerve such as the brachial plexus or from stimulation of the posterior hypothalamus were greatly diminished and sometimes even reversed. Similar results were obtained in the present study, in which noradrenaline was used.

The magnitude of the change of reactivity induced by noradrenaline-tuning is often astonishing. In the experiment illustrated in Figure 10*E* the hypothalamic stimulus used increased the blood pressure by almost 60 mm. Hg. This effect began during the period of stimulation and continued for some time afterward, while the intensive and prolonged acceleration of the pulse rate and the contraction of the nictitating membrane that took place confirmed the intensity of the sympathetic excitation. When the stimulus was reapplied at the height of the noradrenaline-induced pressor phase, the pressor effect was absent. Immediately following the period of stimulation a sharp fall of the blood pressure occurred (Fig. 10*A*, *D*). At the same time, the other sympathetic effects were greatly diminished.

Another example of this reversal effect is illustrated in Figure 18. The hypothalamic stimulus elicited a clear pressor effect under control conditions (*A*, *D*), whereas it elicited no such effect during the state of noradrenaline-induced parasympathetic tuning. Here again, during the poststimulatory period, a sharp fall of the blood pressure occurred, in this instance associated with a few very slow pulses (*B*).*

The phenomena of the reversal of the response to hypothalamic sympathetic stimulation illustrated by these examples were seen with greatest clarity and regularity during the noradrenaline-induced parasympathetic tuning. As Figure 12 shows, they also occurred in other forms of increased blood pressure (like that following histamine hypotension) which may reflexly induce (via the sino-aortic receptors) a state of parasympathetic dominance. However, as was emphasized earlier, the autonomic parasympathetic tuning that results from the conditions of increased blood pressure following upon acetylcholine or histamine hypotension is not pure, since the preceding sympathetic discharge still continues. This "impurity" accounts for the fact that the reversal reaction, if it occurs (as shown in Fig. 12), is ordinarily rather weak; and Figure 16 shows that a reversal reaction may occur in the same preparation during a noradrenaline-induced hypertension but not in the corresponding histamine test.*

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* The time relations are difficult to recognize in the reduced figures when, as in this experiment, the duration of the stimulus was very brief. That the description given in this and similar experiments (Figs. 7, 23) of what happened during the stimulation, in contrast to what occurred after, is correct was ascertained by direct observation during the experiment and also by recording on a fast-moving paper.

A study of Figure 19 should help one understand the mechanism underlying the reversal process. The hypothalamic stimulus applied in this experiment exerted a biphasic action on the blood pressure—a depressor phase preceding a pressor phase; a sympathetic acceleration of the pulse rate continued through both phases (*B*, *D*). Apparently both parasympathetic *and* sympathetic discharges were elicited by the hypothalamic stimulation. When this stimulus was repeated during a noradrenaline-induced pressor phase, the depressor effect was greatly emphasized and the pressor effect was practically abolished.

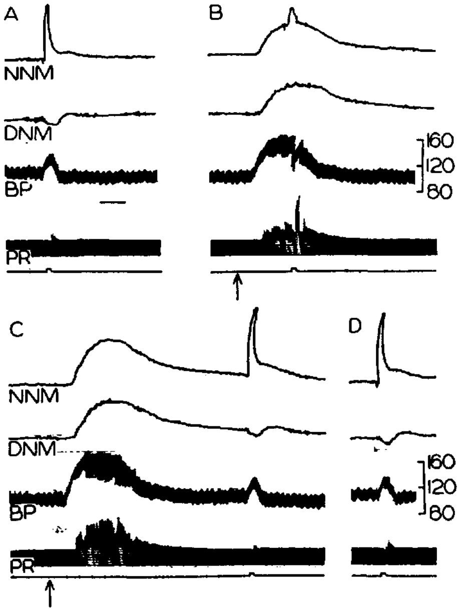

*Figure 18.* Reversal of the hypothalamically induced blood pressure effect under conditions of noradrenaline tuning (injection indicated by the arrows). Note also the greatly reduced contraction of the nictitating membrane (in *B*).

Chloralose 65 mg/Kg and urethane 400 mg/Kg. *A*. Right posterior hypothalamic stimulation (S.W.D., 1 v., 67 pps, 0.8 ms. for 2 sec.). *B*. 2 gammas of noradrenaline i.v. in combination with right posterior hypothalamic stimulation as in *A*. The hypothalamic stimulus was applied at the maximum of the blood pressure. *C*. 3 gammas of noradrenaline i.v. with right posterior hypothalamic stimulation as in *A* during the "undershooting" of the blood pressure. *D*. Same as *A*.

* Note that the blood pressure reaches the same top level in the histamine and noradrenaline tests in this experiment.

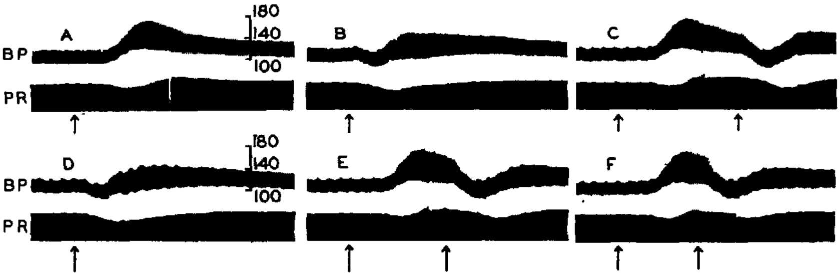

*Figure 19.* The action of a hypothalamic stimulus during noradrenaline-induced hypertension. The hypotensive action of the hypothalamic stimulus is aggravated and the hypertensive action is diminished.

*A*. 2 gammas of noradrenaline i.v. (injection indicated by the arrow). *B*. Bipolar hypothalamic stimulation (indicated by the arrow) (1.5 v., 51 pps, 0.8 ms. for 10 sec.). Electrodes localized in left nucleus infundibularis. *C*. 2 gammas of noradrenaline i.v. (first arrow) followed by hypothalamic stimulation as in *B* (second arrow) during increased blood pressure. *D*. Hypothalamic stimulation by itself, as in *B*. *E*. 2 gammas of noradrenaline i.v. (first arrow) followed by hypothalamic stimulation (second arrow) as in *B* during increased blood pressure, but earlier than in *C*. *F*. 2 gammas of noradrenaline i.v. (first arrow) followed by hypothalamic stimulation (second arrow) as in *B*, during increased blood pressure but earlier than in *E*.

A closer study of Figure 19 reveals this reversal phenomenon in all three tests (*C*, *E*, *F*), but differences occurred in the accompanying sympathetic effects on the pulse rate. Sympathetic effects were most marked in test *C* (relatively late after the injection of noradrenaline) and least marked in test *F*, when the hypothalamic stimulus was applied early during the noradrenaline-induced hypertension, i.e., at a time when the parasympathetic tuning was most pronounced. As the state of parasympathetic tuning diminished, the tendency to a reversal of the blood pressure in response to a hypothalamic sympathetic stimulus was lessened and the sympathetic effects on the heart rate became more distinct.

Although the reversal in response to reflex stimuli or to the direct excitation of central autonomic structures such as the hypothalamus reveals a fundamental change in the reactivity of autonomic centers, it must be stressed that such a reversal may occur in one organ (blood vessels) without affecting another (heart). Here we find yet another illustration that generalizations concerning the functional behavior of the autonomic nervous system as a whole are very dangerous!

Stimuli acting on the hypothalamus are known to elicit parasympathetic as well as sympathetic effects. Thus a stimulus applied to the posterior hypothalamus may call forth a contraction of the nictitating membrane (sympathetic) and a fall of the blood pressure (parasympathetic). Not infrequently the contraction of the nictitating membrane occurs immediately upon stimulation, *before* the blood pressure falls. It cannot, therefore, be due to reflex effects elicited by the fall of the blood pressure; rather, the two effects seem to be an expression of the fact that the same stimulus activates partly sympathetic and partly parasympathetic functions.

It is suggested that the reversal of autonomic effects during parasympathetic tuning is due to the selectively increased parasympathetic excitability, which facilitates the appearance of the parasympathetic action of a hypothalamic stimulus obscured under control conditions.

## 5. Sino-Aortic Reflexes, Tuning, and Autonomic Summation Processes

In view of the fact that any change in the systemic blood pressure (and thereby in the sino-aortic pressure) elicits vascular reflexes which profoundly alter the state of excitability of the autonomic "centers" and their rate of discharge, a thorough experimental analysis of these reflexes is needed. The task set here is threefold:

1. To prove the dependence on sino-aortic reflexes of autonomic tuning produced by hypotensive drugs of the acetylcholine group and histamine and also by hypertensive drugs such as adrenaline and noradrenaline.
2. To demonstrate the modifying influence of sino-aortic reflexes on autonomic summation processes.
3. To show certain limitations of the rules governing autonomic tuning in different organs.

### a. AUTONOMIC TUNING AND SINO-AORTIC REFLEXES

The increased responsiveness of the autonomic system to sympathetic stimuli that occurs during the drug-induced hypotension was thought to result from the decreased activity of the sino-aortic receptors. To test the correctness of this concept experiments were performed to study the effect of autonomic tuning after sino-aortic denervation. Since in the cat the depressor nerves cannot be separated from the efferent vagal nerves in the neck, the denervation eliminated vagal effects on the heart. The heart beat was consequently very fast and showed no changes or minimal changes under the various experimental conditions. It is therefore omitted from the records.

Figure 20 shows the effect of a posterior hypothalamic stimulus on the blood pressure and nictitating membrane under control conditions (*A*, *D*) and during acetylcholine-induced (*B*) and histamine-induced (*C*) hypotension. Whereas under these conditions in control animals with intact sino-aortic receptors (cf. especially the experiment illus-

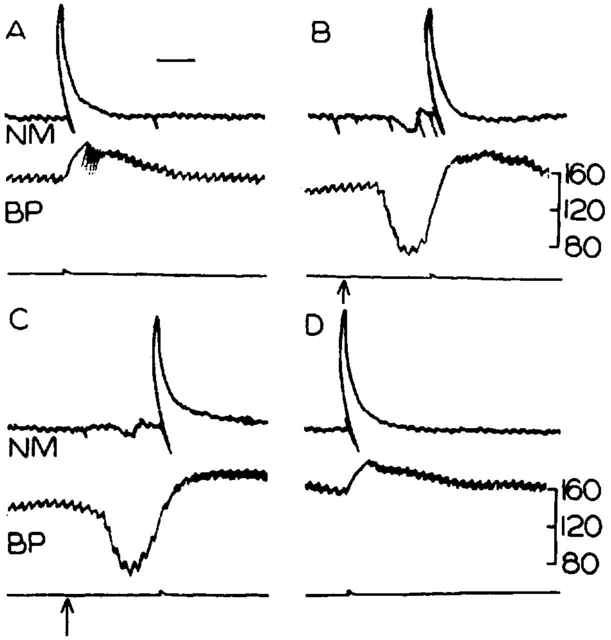

*Figure 20.* The effect of hypothalamic stimulation during acetylcholine and histamine-induced hypotension (injections indicated by the arrows) after sino-aortic denervation. Note that the elimination of the baroreceptors abolishes the sensitization to sympathetic stimuli during hypotension.

Chloralose 65 mg/Kg i.v. *A*. Right posterior hypothalamic stimulation (S.W.D., 0.6 v., 99 pps, 0.8 ms. for 0.5 sec.). *B*. 5 gammas of acetylcholine i.v. in combination with right posterior hypothalamic stimulation. *C*. 20 gammas of histamine i.v. in combination with right posterior hypothalamic stimulation as in *A*. *D*. Same as *A*.

trated in Figure 21, which was performed on the same cat before the sino-aortic denervation) the effectiveness of the hypothalamic stimulus on the nictitating membrane was increased greatly, this was not the case after these receptors had been eliminated. As a matter of fact, the height of the contraction of the nictitating membrane (Fig. 20*B*, *C*) was slightly below that recorded in the control tests (Fig. 20*A*, *D*). The slight reduction in the responsiveness of the hypothalamus that is thus indicated may be due to the lower blood pressure during the acetylcholine- and histamine-induced hypotensive phase.

Figure 22 permits a study of the effect of a hypothalamic stimulus during the noradrenaline tuning before and after sino-aortic denervation. As already discussed, the upper series of graphs shows that the hypothalamic stimulus elicited a much smaller contraction of the nictitating membrane when it was applied at the height of the nor-

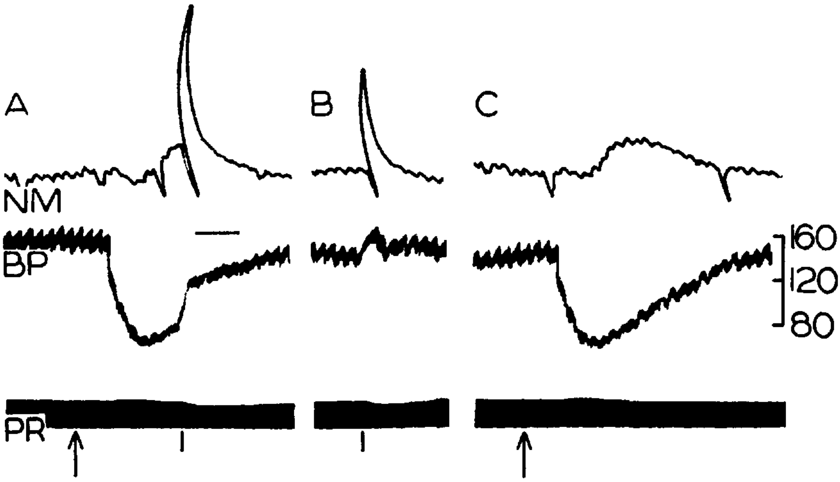

*Figure 21.* The effect of hypothalamic stimulation during acetycholine-induced hypotension (injection indicated by arrows) before sino-aortic denervation. Note the increased sympathetic reactivity indicated by the greatly increased contraction of the nictitating membrane and the abrupt rise of the blood pressure from the hypotension (in *A*).

*A*. 10 gammas of acetylcholine i.v. in combination with right posterior hypothalamic stimulation (indicated by a short vertical line) (S.W.D., 0.6 v., 99 pps, 0.4 ms. for 2 sec.) at the beginning of the recovery of the blood pressure. *B*. Right posterior hypothalamic stimulation as in *A*. *C*. 10 gammas of acetylcholine i.v.

adrenaline-induced pressor effect (*B*) than when it was given under control conditions (*A* and *C*). This startling effect was absent when the experiment was repeated after sino-aortic denervation (*D* to *F*). On closer inspection of the figure one sees after sino-aortic denervation again a slight difference between the contractions of the nictitating membrane that occurred on hypothalamic stimulation in the control test (*E*) and during noradrenaline-induced hypertension (*D* and *F*). In the latter condition the contraction was slightly larger, a result one would expect if in the sino-aortic denervated animal the responsiveness of the hypothalamus to electrical stimulation is directly related to the level of the blood pressure.

The experiments lead to the conclusion that the increased sympathetic responsiveness of the hypothalamus in drug-induced hypotension and the converse effect in drug-induced hypertension are abolished after sino-aortic denervation. *The hypotension induced by mecholyl, acetylcholine, and histamine tunes the autonomic centers sympathetically; the hypertension induced by noradrenaline, etc., tunes the autonomic centers parasympathetically through the sino-aortic reflexes.*

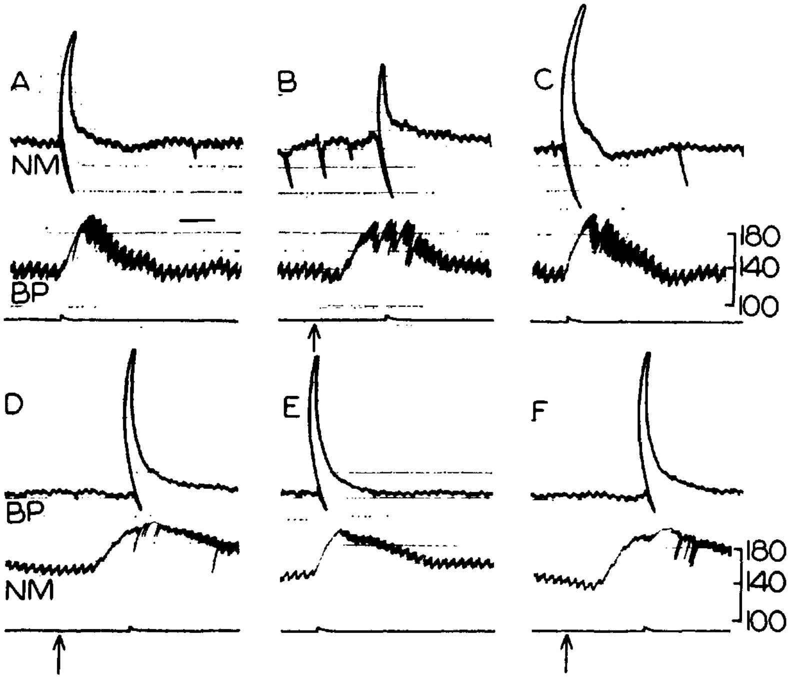

*Figure 22.* The action of hypothalamic stimulation during noradrenaline-induced hypertension (injection indicated by the arrows) before (*A* to *C*) and after sino-aortic denervation (*D* to *F*). Whereas the hypothalamic sympathetic reactivity is reduced in the normal cat during the noradrenaline-induced pressor effect (see the nictitating membrane in *B*), this effect is abolished after sino-aortic denervation (compare the nictitating membrane in *D* and *F* with the control in *E*). [In *D* read NM for BP and BP for NM.]

Chloralose 65 mg/Kg i.v. *A*. Right posterior hypothalamic stimulation (S.W.D., 0.6 v., 99 pps, 1.6 ms. for 0.5 sec.). *B*. 2 gammas of noradrenaline i.v. in combination with right posterior hypothalamic stimulation. *C*. Same as *A*. *D*. 2 gammas of noradrenaline i.v. in combination with right posterior hypothalamic stimulation. *E*. Right posterior hypothalamic stimulation, by itself. *F*. 2 gammas of noradrenaline i.v. in combination with right posterior hypothalamic stimulation as in *D*.

### b. REVERSAL AND INHIBITION OF CENTRALLY INDUCED SYMPATHETIC EXCITATION THROUGH SINO-AORTIC REFLEXES

It was shown that on hypothalamic sympathetic stimulation, applied at the height of a noradrenaline- or adrenaline-induced hypertension, two phenomena occur: (a) the effectiveness of the sympathetic stimulus is reduced; (b) reversal phenomena take place. The reduction of the effectiveness of the sympathetic stimulus may appear, to varying degrees, in a marked lessening of the contraction of the nictitating membrane and a diminution or absence of the pressor effect and of the acceleration of the pulse rate. The reversal phenomenon, particularly distinct immediately following the period of stimulation, is recognized by the fact that the stimulation elicits parasympathetic effects on the blood pressure and pulse rate instead of the sympathetic action seen under control conditions.

The question arises now whether or not similar inhibitory and even reversal phenomena will take place when, as the result of stimulation of central sympathetic structures, a marked rise of the blood pressure is produced which evokes sino-aortic reflexes secondarily.

Figure 23 illustrates a typical experiment. In *B* and *C* the effects of two hypothalamic stimuli acting on the left and right hypothalamus respectively are shown when each stimulus was applied singly. Each of the stimuli elicited typical sympathetic effects on the blood pressure, nictitating membrane, and pulse rate, although quantitatively to quite different degrees. When the two stimuli were applied successively, as illustrated in *A*, so that the second stimulus was administered at the maximum of the pressor effect induced by the first stimulus, the following phenomena occurred: (a) The contraction of the nictitating membrane in response to the second stimulus was very much less than the contraction in response to the same stimulus when applied singly (*B*). (b) The second stimulus failed to raise the blood pressure and to increase the pulse rate during the period of stimulation, although these effects were very great under control conditions (*B*). (c) Immediately upon the cessation of stimulation the blood pressure fell abruptly (reversal) and the pulse rate showed at the same time a phase of slowing absent in the corresponding control test.

This experiment shows that under conditions of a centrally (sympathetically) induced hypertensive phase, there occur inhibitory and reversal phenomena similar to those seen when the blood pressure is raised by a peripherally acting stimulus such as noradrenaline or adrenaline. *The decisive factor is the rise of the pressure in the sino-aortic area and not the specific cause of this alteration in pressure.*

This interpretation is supported by the observation that in the same preparation the degree of inhibition of the contraction of the nictitating membrane and the occurrence or absence of reversal phenomena are correlated with the pressor effect exerted by the first stimulus. In the experiment illustrated in *D* to *F* of Figure 23, the first stimulus was the same as, and the second stimulus very similar to, the stimuli employed in the experiment shown in *A* to *C* of the same figure. The chief difference between the two experiments is that in the one shown in Figure 23*E* the second stimulus was applied a little earlier, i.e., at a time when the blood pressure rise had not reached its maximum.

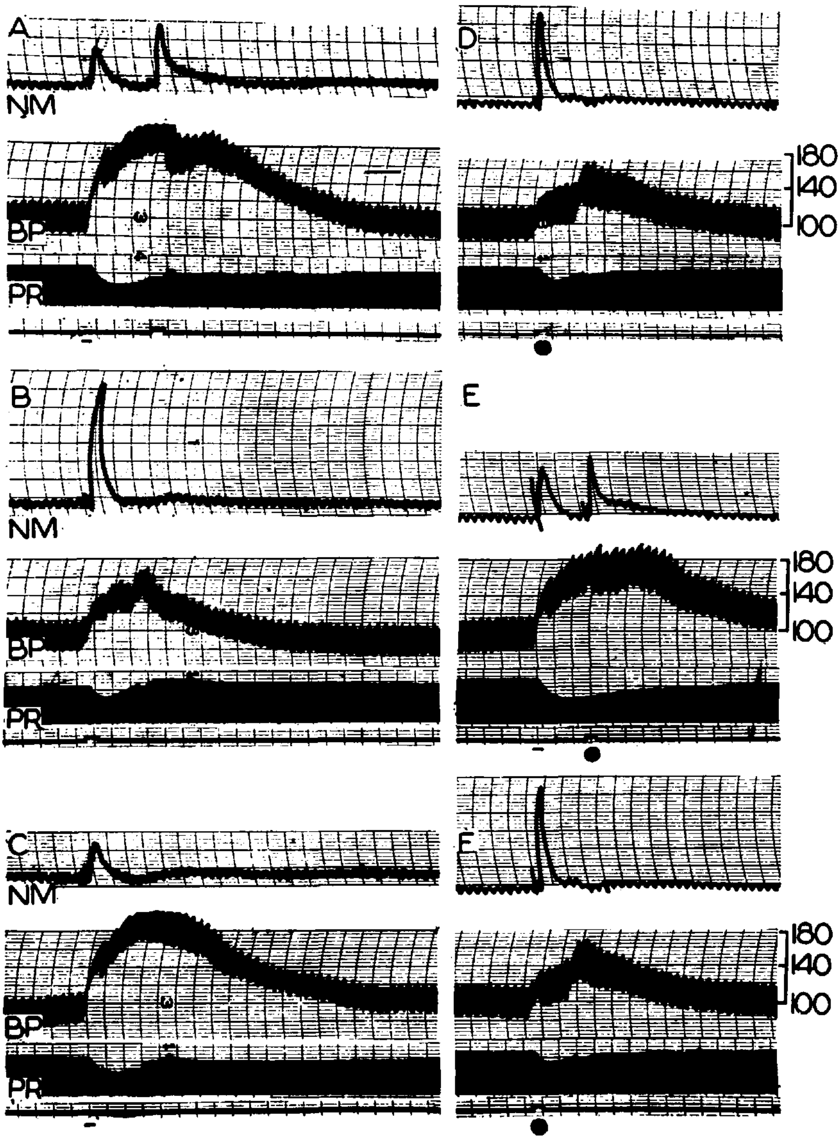

*Figure 23.* Reversal of the hypothalamically induced pressor response during the hypertensive phase induced by hypothalamic stimulation and diminution of the sympathetic reactivity as indicated by the size of the contraction of the nictitating membrane (see *A*). (For further details see the text.)

Chloralose 85 mg/Kg and urethane 200 mg/Kg. *A*. Right posterior hypothalamic stimulation (C.D., 2.5 v., 100 pps, 2 ms. for 4 sec.) in combination with left posterior hypothalamic stimulation (S.W.D., 1.8 v., 74 pps, 0.8 ms. for 3 sec.) given at the blood pressure maximum. *B*. Left posterior hypothalamic stimulation as in *A*. *C*. Right posterior hypothalamic stimulation as in *A*. *D*. Left posterior hypothalamic stimulation (1.5 v., 99 pps, 0.4 ms. for 3 sec.). *E*. Right posterior hypothalamic stimulation (2.5 v., 100 pps, 2 ms. for 4 sec.) in combination with hypothalamic stimulation as in *D*. *F*. Left posterior hypothalamic stimulation as in *D*.

Under these conditions the reduction in the contraction of the nictitating membrane in response to the second stimulus was much less than than under the conditions shown in the left half of Figure 23. Moreover, the pulse slowing failed to occur, and the fall of the blood pressure immediately after the stimulus was almost absent. Apparently a reversal of sympathetic phenomena takes place only when the sino-aortic pressure is excessive.

Although the modifying action on the reactivity of the autonomic nervous system induced by a given rise of the pressure in the sino-aortic area is similar in principle whether this rise is effected by the injection of noradrenaline or by hypothalamic stimulation, there are marked quantitative differences between the two types of rise in the degree of modifying action. This matter will be discussed later. Suffice it to state now that in conditions where central sympathetic stimuli interact, the regulatory processes evoked by the rise of the blood

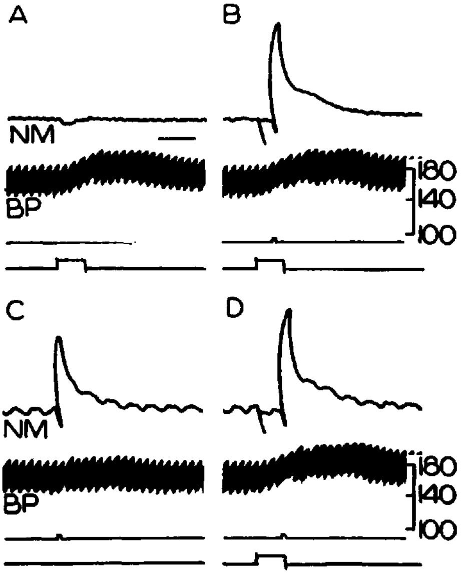

*Figure 24.* The interaction of hypothalamic stimuli after sino-aortic denervation. Note that the sympathetic response indicated by the nictitating membrane is increased during the hypertensive phase (see *B* and *D*).

Chloralose 65 mg/Kg and urethane 400 mg/Kg i.v. *A*. Left posterior hypothalamic stimulation (C.D., 3.3 v., 100 pps, 2 ms. for 10 sec.). *B*. Left posterior hypothalamic stimulation as in *A* in combination with left posterior hypothalamic stimulation (S.W.D., 1.5 v., 99 pps, 1.6 ms. for 1 sec.) 5 seconds after *A*. *C*. Left posterior hypothalamic stimulation (S.W.D., 1.5 v., 99 pps, 1.6 ms. for 1 sec.) by itself. *D*. Left posterior hypothalamic stimulation as in *A* in combination with left posterior hypothalamic stimulation as in *C*, but 8 seconds after *A*.

pressure resulting from one stimulus alter quantitatively and qualitatively the action of another hypothalamic sympathetic stimulus. Through inhibition and reversal, such regulations seem to limit excessive degrees of sympathetic excitation.

This interpretation is supported by experiments such as that illustrated in Figure 24, in which after sino-aortic denervation these inhibitory phenomena no longer occur. Since the blood pressure is very high after denervation, the conditions would be favorable for inhibitory phenomena if these originated in structures other than the sino-aortic receptors. Nevertheless these modifying influences are absent, and Figure 24 shows that only the typical summation and potentiation processes, particularly on the nictitating membrane, remain.

### C. MODIFICATION OF AUTONOMIC SUMMATION PROCESSES THROUGH SINO-AORTIC REFLEXES

The foregoing experiments have shown that changes in the blood pressure regardless of the nature of the causative agent may greatly modify the responsiveness of the autonomic system. These findings have a wider application than has yet been indicated. They seem to account for alterations of autonomic reactivity induced by changing the blood volume* and also for unexpected results in experiments involving an interaction between parasympathetic and sympathetic stimuli.

Figure 25 illustrates an experiment on the interaction of sciatic and hypothalamic stimulation. The hypothalamic stimulus elicited the triad of sympathetic effects on the nictitating membrane, blood pressure, and pulse rate noted in *C*. A sciatic stimulus of low frequency, on the other hand, produced parasympathetic effects, as shown in *B*. The blood pressure fell gradually; only, when it returned from this slight hypotension, it overshot a little and the pulse rate slightly accelerated—clearly sino-aortic reflex-effects. When during the parasympathetic phase resulting from sciatic stimulation the hypothalamic stimulus was applied (*A*, *D*), the contraction of the nictitating membrane was distinctly increased.†

This result may at first glance appear paradoxical. Since central summation processes determine the phenomena resulting from the interaction of two stimuli, the effectiveness of a sympathetic stimulus ought to be diminished by the simultaneous action of an antagonistic parasympathetic stimulus. Certain interactions described earlier (for instance, those operating on the heart rate as shown in Figure 14) may

* See p. 43.

† There is also a more rapid rise of the blood pressure to be seen in *A* and *D* than in *C*!

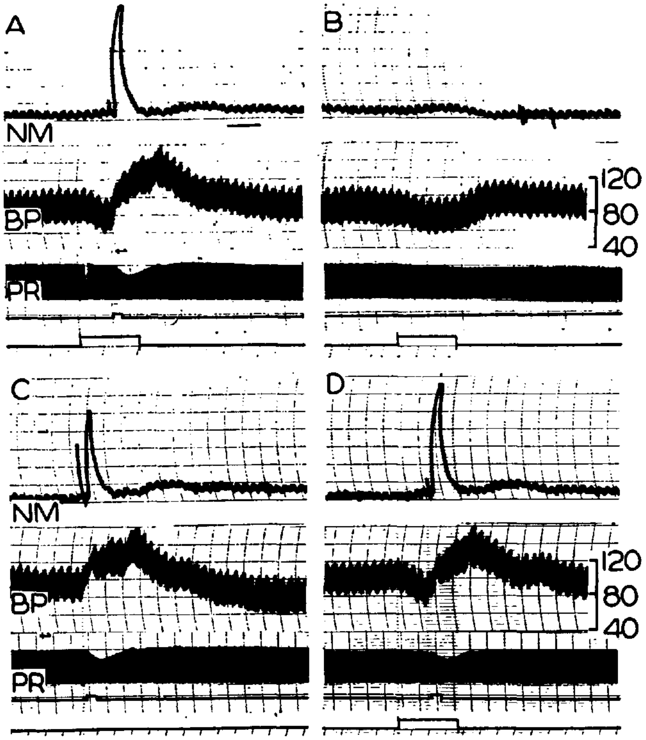

*Figure 25.* The interaction of stimulation of the sciatic nerve (parasympathetic type) with hypothalamic stimulation (sympathetic type). The contraction of the nictitating membrane shows that the sympathetic reactivity is increased while the blood pressure is lowered through a parasympathetically acting stimulation of the sciatic nerve.

Chloralose 85 mg/Kg and urethane 200 mg/Kg. *A*. Sciatic stimulation (C.D., 4.4 v., 15.2 pps, 2 ms. for 20 sec.) in combination with left posterior hypothalamic stimulation (C.D., 1.8 v., 74 pps, 0.4 ms. for 3 sec.). *B*. Sciatic stimulation by itself. *C*. Left posterior hypothalamic stimulation. *D*. Combined sciatic and hypothalamic stimulation as in *A*.

well be used as an illustration of these rules. The seeming exception to the rule of summation suggests that another factor was operative in the experiment illustrated in Figure 25.

The explanation of the experimental findings lies in the tuning action of the sciatic stimulus. The (slight) fall of the blood pressure * produced a sympathetic reflex tuning via the sino-aortic receptors. The hypothalamic stimulus (sympathetic type) therefore became more effective and caused an increased contraction of the nictitating membrane. If this tuning of the autonomic nervous system via the sino-aortic receptors is what was decisive for the action of the test stimulus, it must have been accomplished through alterations in the pressure in the sino-aortic area. It would, therefore, be independent of whether a change in pressure resulted from drug or reflex action or from a direct excitation of autonomic centers such as the hypothalamus.

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* Resulting from sciatic stimulation.

This conclusion is confirmed by the experiment illustrated in Figure 26, in which the direct excitation of the hypothalamus served as the tuning stimulus (*C*). Here again a stimulus of the parasympathetic type was chosen. The effect on the blood pressure and especially on the pressure at the sino-aortic receptors seems to have been similar to that produced in the experiment shown in Figure 25, and the fundamental results are similar in both experiments. Figure 26*C* shows that the first and rather prolonged hypothalamic stimulus elicited a parasympathetic action (fall of the blood pressure), whereas the sec-

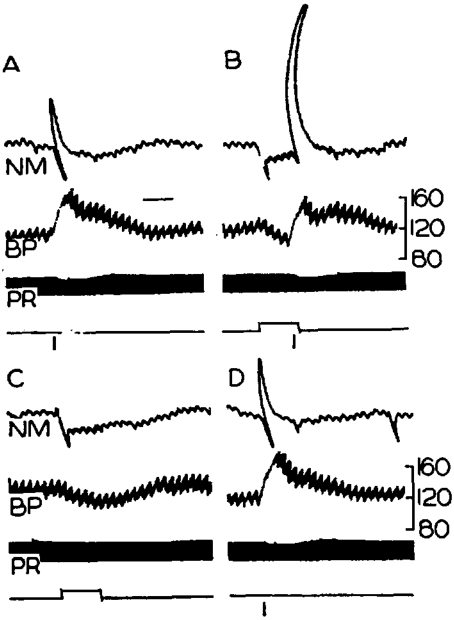

*Figure 26.* The interaction of two hypothalamic stimuli which exert a parasympathetic and sympathetic reaction, respectively. While the blood pressure is lowered through a parasympathetically acting hypothalamic stimulus, the reactivity of the nictitating membrane to sympathetic stimulation is increased.

Chloralose 65 mg/Kg i.v. *A*. Left posterior hypothalamic stimulation, site 1, sympathetic type (S.W.D., 6.6 v., 99 pps, 0.8 ms. for 0.5 sec.). *B*. Left posterior hypothalamic stimulation, site 3, (C.D., 1.5 v., 30 pps, 4 ms. for 15 sec.) in combination with left posterior hypothalamic stimulation, site 1, as in *A* after 14 seconds. *C*. Left posterior hypothalamic stimulation, parasympathetic type, site 3, as in *B*. *D*. Same as *A*.

ond, brief hypothalamic test stimulus evoked the above-mentioned sympathetic triad, seen in *A* and *D*. On combination of the two stimuli (administered in such a manner that the hypothalamic test stimulus was applied *after* a slight fall of the blood pressure had been established by the parasympathetic hypothalamic stimulus) the contraction of the nictitating membrane was greatly increased (*B*).

*The experiments show that sympathetic hypothalamic responsiveness is enhanced when, by direct stimulation of the hypothalamus or through reflexes elicited by sciatic stimulation, a slight fall in blood pressure is induced. It is suggested that here again a form of sympathetic tuning via sino-aortic reflexes is involved.*

### d. HEMORRHAGE AND AUTONOMIC TUNING

When an animal is bled moderately, several stages indicating alterations of autonomic activity may be distinguished. At first there may be no change in the blood pressure, but the pulse rate is increased; later a progressive fall of the blood pressure is associated with a progressive acceleration of the heart rate. It may be assumed that at first a temporary fall of the sino-aortic pressure elicits sympathetico-adrenal reflexes which restore the blood pressure and maintain a somewhat increased heart rate; at later stages these reflexes cannot fully compensate for the loss of blood: the blood pressure remains lower, and this fall is commonly associated with an increased pulse rate. If under these conditions a hypothalamic sympathetic stimulus is applied, it elicits a greater sympathetic effect than under control conditions. This increased sympathetic effect, however, may be confined to the blood pressure and nictitating membrane; it may not alter the responsiveness of the pulse rate if the pulse rate was already greatly increased before the stimulus was applied.

Figure 27 illustrates an experiment in which a moderate loss of blood led to a considerable fall of the blood pressure; no significant change in the pulse rate occurred. The responsiveness to a given hypothalamic stimulus was greatly altered. A comparison between *A* and *B* of Figure 27 shows that the stimulus elicited a much greater sympathetic response after the bleeding, as indicated by the greater contraction of the nictitating membrane, the acceleration of the pulse rate, and the magnitude and duration of the rise of the blood pressure. It is probable that the increased sympathetic effects on the vascular system were in part due also to the weakened parasympathetic reflexes, since pulse slowing occurs only when the blood pressure reaches a certain absolute level. After bleeding with the pressure lowered, therefore, parasympathetic reflexes are commonly weak or absent.

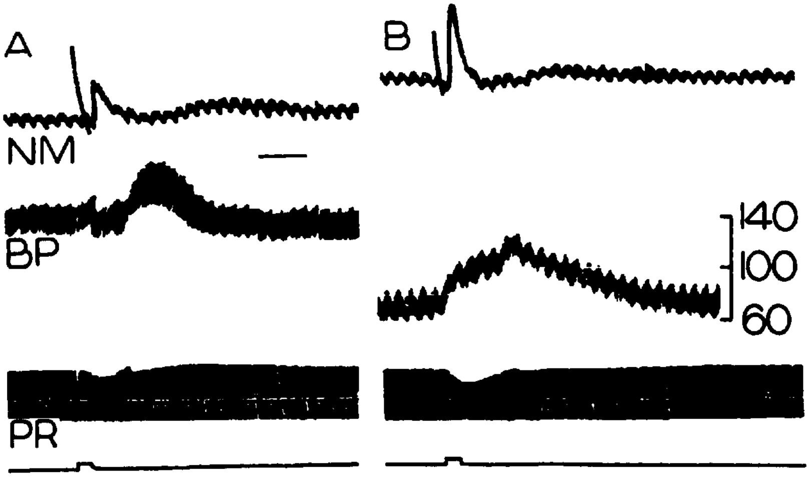

*Figure 27.* Hemorrhage and sympathetic reactivity. Note that the sympathetic responsiveness (indicated by the blood pressure, the nictitating membrane, and the heart rate) to hypothalamic stimulation is increased after bleeding.

Chloralose 85 mg/Kg and urethane 200 mg/Kg. *A*. Left posterior hypothalamic stimulation (S.W.D., 1.8 v., 74 pps, 0.4 ms. for 3 sec.). *B*. Left posterior hypothalamic stimulation as in *A* given after 20 cc. of blood had been removed.

### e. DEXTRAN AND AUTONOMIC TUNING

Figure 28 illustrates the effect on the responsiveness of the parasympathetic system of the injection of 20 cc. of dextran, the capacity of which to raise the blood pressure and counteract shock is well established (294). Two gammas of noradrenaline were used as a test stimulus; the effect on the blood pressure and pulse rate reveals a very great increase in parasympathetic reflex responsiveness. Whereas in the control test (Fig. 28*A*) the blood pressure, upon the injection of noradrenaline, declined gradually and smoothly, except for a minor dip, from the maximal pressure, very abrupt dips appear repeatedly in the analogous test (Fig. 28*B*) performed after the blood pressure had been raised by dextran. This record shows clearly that the parasympathetic reflexes elicited by the rise of the blood pressure and consequently of the pressure in the sino-aortic area were much more powerful after the injection of dextran. In addition, each of the parasympathetic phases of the blood pressure curve was accompanied by marked bursts of pulse deceleration, whereas under control conditions only a minimal slowing of the pulse rate occurred. Such gradual slowing, obviously a parasympathetic reflex induced by the rise of the blood pressure, was present also in the test after the injection of dextran (*B*), and on it were superimposed the phasic parasympathetic reflexes described above. It is noteworthy that these profound changes in the reactivity of the parasympathetic system resulted from an injection of dextran which raised the blood pressure by only 20 mm. Hg.* Both tests were performed while the blood pressure levels remained within physiological limits, and the relative increase in the

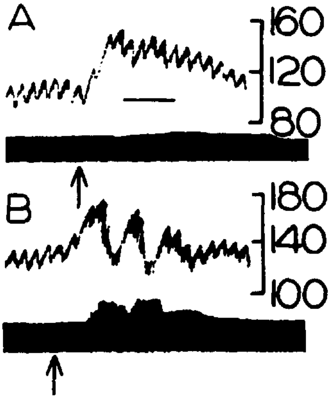

*Figure 28.* Blood pressure level and parasympathetic reactivity. Note the great increase in parasympathetic reflex activity which occurs in response to noradrenaline (injection indicated by the arrow) when the blood pressure has been elevated by the injection of dextran.

Chloralose 65 mg/Kg i.v. The injection of 2 gammas of noradrenaline i.v. is indicated by the arrow. Between *A* and *B* 20 cc. of dextran was administered intra-arterially.

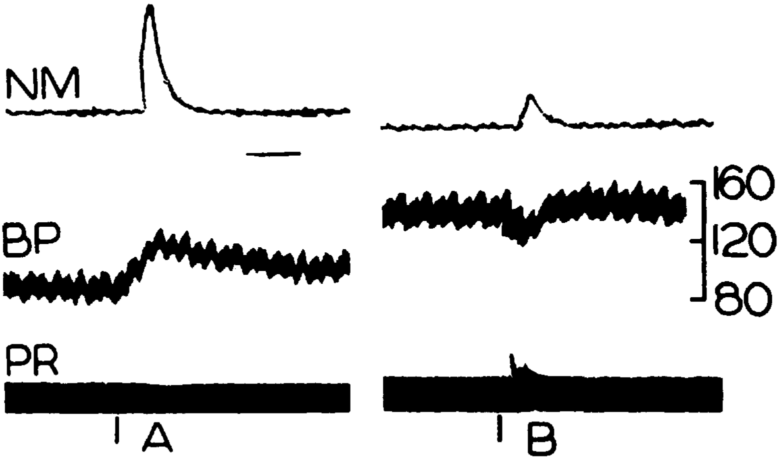

*Figure 29.* Blood pressure level and sympathetic reactivity. Note the reversal of the blood pressure and the lessened sympathetic response (nictitating membrane) to hypothalamic stimulation after the blood pressure has been raised by the injection of dextran.

Chloralose 65 mg/Kg and urethane 400 mg/Kg. *A*. Left posterior hypothalamic stimulation (C.D., 3 v., 100 pps, 2 ms. for 5 sec.). *B*. Left posterior hypothalamic stimulation as in *A* after the blood pressure level has been increased by the injection of 20 cc. of dextran intra-arterially.

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* The greater amplitude of the pulse record in Figure 28*B* shows that the pulse rate has been lowered at the same time.

pressure resulting from the injection of noradrenaline was about the same.

In the experiment illustrated in Figure 29 the change in the level of the blood pressure was considerably greater (from about 90 to 140 mm. Hg). In the control test the sympathetic hypothalamic stimulus produced the often described triad of effects, a prolonged rise of the blood pressure with a slight acceleration of the heart rate and a contraction of the nictitating membrane. After the blood pressure level had been raised, this stimulus caused only a minimal contraction of the nictitating membrane and a reversal of the action on blood pressure and pulse rate seen under control conditions. Instead of sympathetic effects on the heart and blood vessels, parasympathetic effects now appear: the blood pressure falls and this fall is associated with a distinct slowing of the heart rate. The experiment shows that after the injection of dextran sympathetic excitability was diminished (as indicated by the action of the test stimulus on the nictitating membrane) and parasympathetic excitability was increased. The second phenomenon appears not only in the greater responsiveness to parasympathetic reflexes but also in the fact that parasympathetic responses are elicited by a stimulus which under control conditions produced only sympathetic effects.

### f. AUTONOMIC TUNING AND BLOOD PRESSURE VARIATIONS INDUCED BY NORADRENALINE

Drugs such as noradrenaline, which represent an important neurohumor, warrant a further investigation of their relation to the reactivity of the autonomic nervous system. It is frequently seen that the pressor phase produced by noradrenaline is followed by a lesser depressor phase, the latter becoming more marked as the dose of noradrenaline is increased. If a sympathetic stimulus is applied during this hypotensive phase, signs of increased responsiveness are seen.

Figure 11 shows at *B* the diminished response of the nictitating membrane to hypothalamic stimulation at the height of the hypertensive phase and at *C* the increased response at the later hypotensive phase. The control tests illustrated in *A* and *D* of the figure show the constancy of the reactivity of our preparation. It is remarkable, and speaks for the physiological significance of these findings, that a distinct increase in the sympathetic responsiveness occurs with a fall of the blood pressure of only 6 or 7 mm. Hg, although such minimal variations when they occur spontaneously are not associated with significant changes in autonomic reactivity. It is therefore suggested

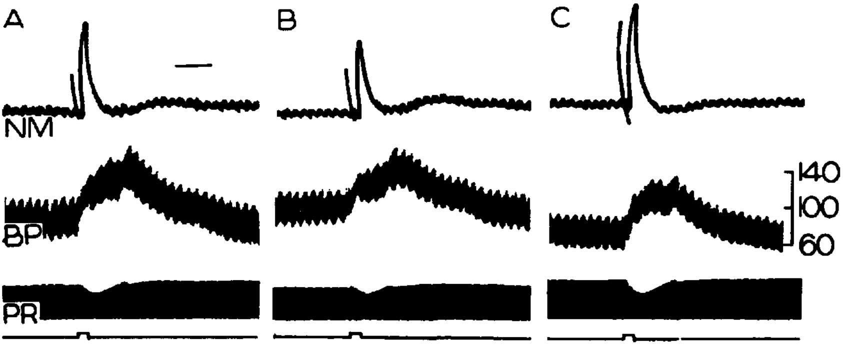

*Figure 30.* The influence of variations in the blood pressure following the injection of noradrenaline on the reactivity to hypothalamic stimulation. The sympathetic response of the nictitating membrane and the heart rate increase as the blood pressure falls.

Chloralose 85 mg/Kg and urethane 200 mg/Kg. *A.* Left posterior hypothalamic stimulation (S.W.D., 1.8 v., 74 pps, 0.4 ms. for 3 sec.), applied during the hypotensive phase which followed the noradrenaline (0.5 gammas i.v.) induced pressor effect. *B.* Left posterior hypothalamic stimulation (control). *C.* Left posterior hypothalamic stimulation as in *A* given during the hypotensive phase which followed the injection of 3 gammas of noradrenaline i.v.

that the injection of noradrenaline (and very probably its secretion in the adrenal medulla) induces first (through an increase in the sino-aortic pressure) a state of parasympathetic dominance and later, as the blood pressure returns to the control level and undershoots this level slightly, a state of sympathetic dominance.

Figure 30 illustrates two other examples of a post-noradrenaline-induced state of increased sympathetic responsiveness. The beginnings of sections *A* and *C* represent the tail end of a post-noradrenaline hypotension induced by the injection of 0.5 and 3 gammas respectively; section *B* represents the control test. Consequently, the blood pressure level is the highest in *B*, intermediate in *A*, and the lowest in *C*. The difference between the blood pressures shown in *A* and *B* was minimal, but between those shown in *B* and *C* it was about 25 mm. Hg. The sympathetic responsiveness showed an increase from *B* to *A* to *C*. This was borne out by the size of the contraction of the nictitating membrane and the degree of acceleration of the heart rate, but not by the magnitude of the pressor response. The rapidity of the rise of the blood pressure, however, was increased in the same order.

The experiments suggest that reflexes leading to alterations in the state of autonomic responsiveness may, before the resting equilibrium is reached again, pass through a state of imbalance of opposite characteristics.*

### g. MUTUAL INFLUENCES BETWEEN THE PARASYMPATHETIC AND SYMPATHETIC SYSTEMS

Our knowledge of the intimate interrelation existing between the two divisions of the autonomic nervous system seems to have been advanced by the study of autonomic reactions under conditions of experimentally induced dominance ("tuning"). An important result of this work was the establishment of the principle of reciprocal innervation for states of an altered autonomic balance. Thus it was shown that sympathetic tuning inhibits parasympathetic action and that parasympathetic tuning inhibits sympathetic effects. From typical changes which occur under the influence of the tuning stimulus, the erroneous impression may arise that "tuning" is, as it were, a one-way affair. This is by no means true, although under certain experimental conditions, i.e., when the autonomic balance is markedly shifted in one direction, only unidirectional changes in excitability seem to occur.

If, however, the tuning stimulus is relatively weak, more complex relations may result, as the following example illustrates. Let us suppose that a weak sympathetic stimulus serves as the "tuning stimulus" and a relatively strong parasympathetic "test stimulus" is applied. Under these conditions one would expect the effect of the "test stimulus" to be modified according to the previously stated rules. It is so modified indeed, but the effect of the "tuning stimulus" is in turn modified by the action of the "test stimulus." The physiological, and also the pathological, significance of this experimental situation seems to lie in the fact that different states of tuning may exist simultaneously in different organs as the result of the interactions of the effects resulting from the two stimuli. This interpretation is suggested by the experiment illustrated in Figure 13, in which noradrenaline was injected while a sympathetic hypothalamic stimulation induced sympathetic tuning. In this familiar condition the noradrenaline-induced parasympathetic reflex on the pulse rate was delayed considerably, but, as Figure 13 shows, the injection of noradrenaline had in its turn a profound influence on the sympathetic effects resulting from hypothalamic stimulation. As noradrenaline became effective in raising the blood pressure, it inhibited the contraction of the nictitating membrane which had been elicited by hypothalamic stimulation. This inhibitory action has been shown to be due to a sino-aortic reflex elicited by the rise of the blood pressure. At present, however, we are not concerned with the mechanism involved, but with the result, the diminution of the contraction of the nictitating membrane. Although numerous experiments have illustrated the fact that sympathetic tuning increases the responses to sympathetic stimulation and diminishes the responses to parasympathetic stimulation, this statement is incomplete: it does not take into consideration the effect of the test stimulus (noradrenaline in this experiment) on the action of the tuning stimulus itself. Although the sympathetic tuning is quite effective in delaying (and often also in decreasing) the parasympathetic responsiveness in one organ (the heart, as indicated by the heart rate in Figure 13*B*), the sympathetic discharge produced by the tuning stimulus (applied to the posterior hypothalamus) is reduced (through the test stimulus) in another organ (the nictitating membrane, as in Figure 13*B*). During the interaction of the two stimuli the sympathetic state of the nictitating membrane is lessened (as in parasympathetic tuning), whereas the development of the reflex slowing of the heart rate is delayed (as in sympathetic tuning).*

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* It would be interesting to repeat these experiments with noradrenaline in conditions in which through mechanical means (Fog's device, 69) any alteration in the blood pressure is prevented.

## 6. THE ACTION OF CHEMORECEPTORS ON THE AUTONOMIC NERVOUS SYSTEM

The preceding investigations have shown that the reactivity of the autonomic nervous system to various stimuli involves summation processes in which somatic (nociceptive) and visceral (sino-aortic baroreceptor) reflexes play an important part. They have also shown that the baroreceptor reflexes modify the responsiveness of the autonomic centers to direct and reflex stimuli according to rather simple rules. These results raise the question of the role of the chemoreceptors in autonomic excitability and also the question whether the responsiveness of autonomic centers may be altered directly by changes in the chemical composition of the blood.

### a. ANOXIA, HYPERCAPNIA, AND HYPOGLYCEMIA AND THE BALANCE OF THE AUTONOMIC NERVOUS SYSTEM

Stimulation of the hypothalamus or medulla oblongata leads to a greater pressor effect during anoxia than during a state of normal oxygenation of the blood (105). If, however, the sino-aortic receptors are eliminated, different results occur. The blood pressure falls in anoxia whereas it rises when the buffer reflexes are intact (124). Moreover, the pressor effect of hypothalamic or medullary stimulation is diminished after sino-aortic denervation. These experiments suggest that during anoxia increased impulses originating in the sino-aortic chemoreceptors summate with those elicited by direct stimulation of the autonomic centers and result in a greater pressor effect than is seen when air is inhaled and the activity of the chemoreceptors is greatly lessened (300).

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* See also p. 70.

When similar experiments are performed to determine the influence of carbon dioxide on the autonomic centers, it is found that the pressor response and also the contraction of the nictitating membrane to stimulation of the medullary or diencephalic autonomic centers is increased; but this effect—in contrast to the action of anoxia—persists after sino-aortic denervation (87). Since carbon dioxide does not alter the responsiveness of the nictitating membrane to stimulation of the peripheral end of the sectioned superior cervical sympathetic nerve, it may be concluded that carbon dioxide increases the excitability of the central autonomic structures. Carbon dioxide increases also the rate of the discharges from the chemoreceptors (300). It appears, therefore, that the increased responsiveness of the autonomic centers during hypercapnia is due in part to an increase in the discharges from the chemoreceptors, which summate with those elicited by direct stimulation of the centers, and is, in part, the result of the action of carbon dioxide on the brain itself.

Yet another type of mechanism seems to underlie the action of hypoglycemia. There is no evidence that the lowering of the blood sugar acts on the chemoreceptors (330). On the other hand, in the hypoglycemic state there is a marked increase in the rise of the blood pressure in response to a given degree of anoxia, and this effect is indirectly related to the level of the blood sugar (118). These observations suggest that increased impulses from the chemoreceptors resulting from anoxia interact, in the hypoglycemic state, with augmented sympathetic impulses originating in the hypothalamus and medulla.

The increased rate of discharge from the autonomic centers during hypoglycemia is evident also from experiments involving the action of carbon dioxide. The increase in the blood pressure induced by carbon dioxide is augmented as the blood glucose concentration is lowered, and this augmentation of the effect persists in animals deprived of the buffer nerves (121). These results again indicate that during hypoglycemia the autonomic centers are in a state of increased excitability which is independent of chemoreceptor reflexes. In the sino-aortic denervated animal, the discharges induced by the action of carbon dioxide on the autonomic centers summate with the increased discharges originating in the hypoglycemic centers.

The purpose of this rather incomplete survey is to point out that autonomic summation processes, which determine the reactivity of the autonomic centers and the state of autonomic balance, are modified not only by the action of pressoreceptors, as shown in the preceding sections of this book, but also by impulses originating in the chemoreceptors and by direct action on the brain itself. As a small contribution to this problem, the responsiveness of the autonomic centers in the state of asphyxia may now be considered.

### b. ASPHYXIA AND AUTONOMIC BALANCE

Asphyxia, conveniently produced in the experimental animal by the clamping of the trachea, leads to a rapid diminution in the oxygenation of the blood and also to an accumulation of carbon dioxide and nonvolatile acids. This change in the internal environment has several effects on the autonomic nervous system. The decrease in the oxygen and the increase in the carbon dioxide tension of the blood leads to an excitation of the sino-aortic chemoreceptors. In addition, the hypoxia acts directly on the autonomic central structures and diminishes their reactivity, whereas the hypercapnia has the opposite effect. Whether hypoxia or hypercapnia supervenes in asphyxia will probably depend on the duration of the asphyxia, the respiratory capacity, the reserve power of the heart, and similar factors. Furthermore, it must be borne in mind that during asphyxia the blood pressure may first rise and then fall. These changes will call baroreceptor reflexes into play.

*(1) The autonomic nervous system in early asphyxia.* During the first 20 to 30 seconds following the beginning of asphyxia one observes that the responsiveness of the sympathetic centers in the hypothalamus and medulla oblongata is increased. Since the nictitating membrane is supplied with sympathetic fibers only, it gives clear evidence of the increased sympathetic reactivity by its augmented contraction in response to a hypothalamic (Fig. 31) or medullary stimulus. The contraction is frequently seen in the normal and not in the denervated nictitating membrane, indicating that the increased responsiveness is confined to the neurogenic discharge and does not involve the humoral activity of the adrenal medulla.* Often the action of the hypothalamic stimulus on the pulse rate and blood pressure is also increased.

The reaction of the heart rate to hypothalamic stimulation may give an insight into the shift of the autonomic balance in asphyxia.

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* The neurogenic discharge involves the liberation of a neurohumor, which, however does not appear in sufficient quantities in the blood to act on denervated structures (see item 94, pp. 232ff).

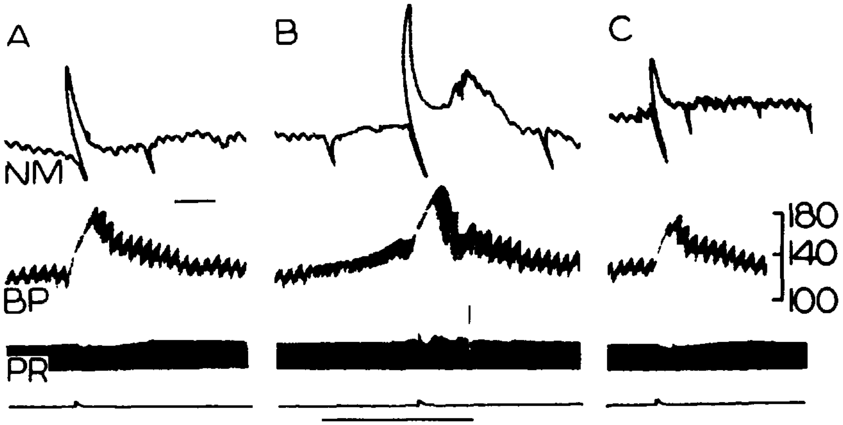

*Figure 31.* Asphyxia and reactivity to hypothalamic stimulation. The sympathetic responsiveness is increased in asphyxia as indicated by the nictitating membrane (in *B*).

Chloralose 65 mg/Kg i.v. *A*. Left posterior hypothalamic stimulation (S.W.D., 0.6 v., 99 pps, 0.4 ms. for 1 sec.). *B*. 40 seconds of asphyxia in combination with left posterior hypothalamic stimulation after 25 seconds. *C*. Same as *A*.

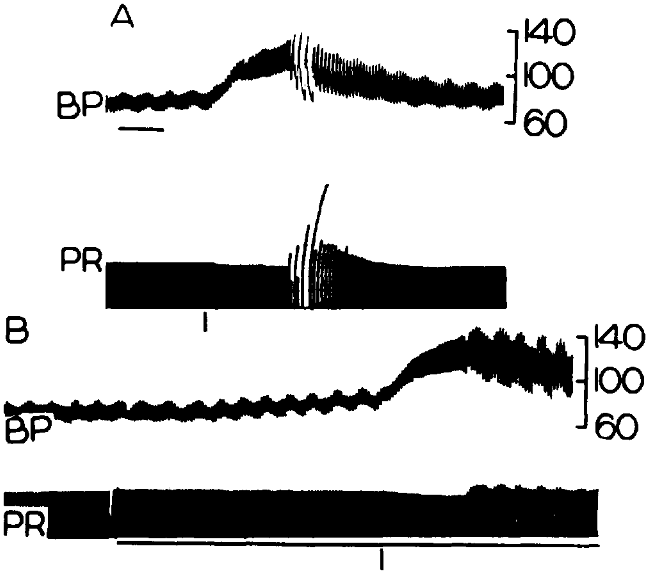

*Figure 32.* Asphyxia and hypothalamic stimulation. Note that the sympathetic reactivity is increased and the parasympathetic responsiveness is decreased in asphyxia, as indicated by the greater pulse acceleration during, and the lesser slowing of the pulse rate following, hypothalamic stimulation.

*A*. Hypothalamic stimulation (2.5 v., 71 pps, 1.6 ms. for 10 sec.) is indicated by a vertical line (horizontal line in *A* = 10 sec.). *B*. 60 seconds of asphyxia in combination with the same hypothalamic stimulus applied 30 seconds after the beginning of asphyxia. Asphyxia is indicated by the long horizontal line below PR.

Figure 32 shows that the acceleration of the heart rate in response to the hypothalamic stimulus is much greater during asphyxia than under control conditions and also that the successive autonomic induction is altered. The parasympathetic discharge that follows the cessation of the stimulus is greatly weakened in asphyxia. This weakening is the more remarkable as several factors would seem to favor an intensified parasympathetic reaction. They are: (a) The greater sympathetic discharge during the stimulation period which occurs in asphyxia. It was noted earlier* that, other conditions being equal, the successive autonomic induction increases with increasing sympathetic stimulation, i.e., with conditions leading to increasing sympathetic discharges. (b) Since under the combined influence of asphyxia and hypothalamic stimulation the blood pressure rises more than

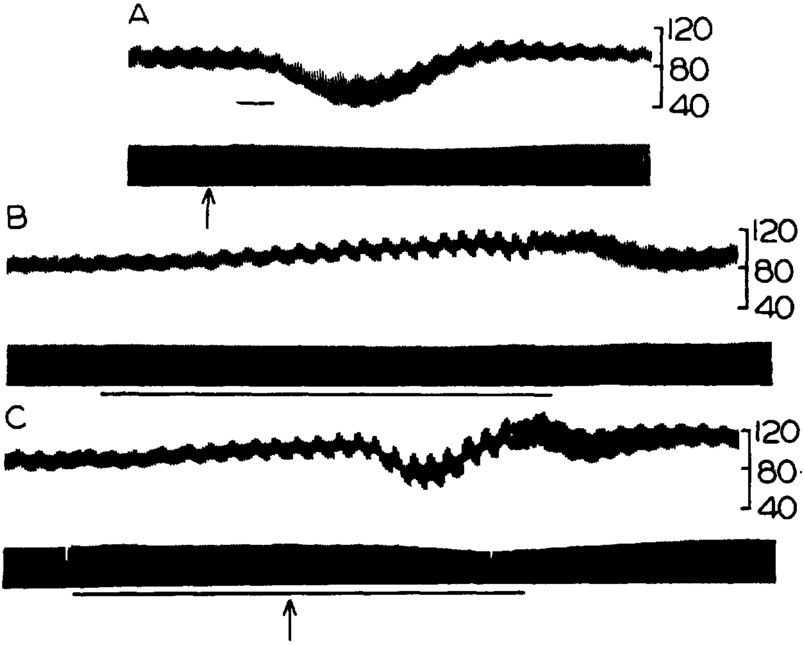

*Figure 33.* The effect of acetylcholine (injection indicated by the arrow) during asphyxia. Acetylcholine elicits stronger sympathetic reflex effects during asphyxia (*C*) than under control conditions (*A*). Note the greater acceleration of the pulse rate and the quicker return of the blood pressure from the hypotensive phase.

*A*. 7.5 gammas of acetylcholine i.v. *B*. 60 seconds of asphyxia. *C*. 60 seconds of asphyxia with 7.5 gammas of acetylcholine i.v. at 30 seconds of asphyxia.

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* See p. 24.

when the hypothalamic stimulus is given alone, the tendency to parasympathetic reflex slowing should increase.

Nevertheless, in the poststimulatory period the pulse rate is slowed much less during asphyxia than in the control state. Apparently asphyxia not only increases sympathetic reactivity but also diminishes parasympathetic reactivity. The autonomic balance shifts to the sympathetic side, and the reciprocal relation that exists physiologically between the excitability of the centers of the two autonomic divisions is maintained at this stage of asphyxia.

There is further evidence that the autonomic balance shifts to the sympathetic side during asphyxia. If acetylcholine or other hypotensive drugs are used in early asphyxia, changes occur in their action on the blood pressure, heart rate, and nictitating membrane which are indicative of an increased sympathetic reactivity. Figure 33 shows that acetylcholine is associated with a much greater acceleration of the pulse rate during asphyxia (*C*) than in the control period (*A*), although asphyxia per se increases the heart rate (*B*) only minimally. Furthermore, the return of the blood pressure from hypotension is greatly accelerated and continues to a distinct hypertensive phase which is practically absent in the control test. As will be discussed in detail later, these changes are similar to those seen when the sympathetic central excitability was raised either by the injection of excita-

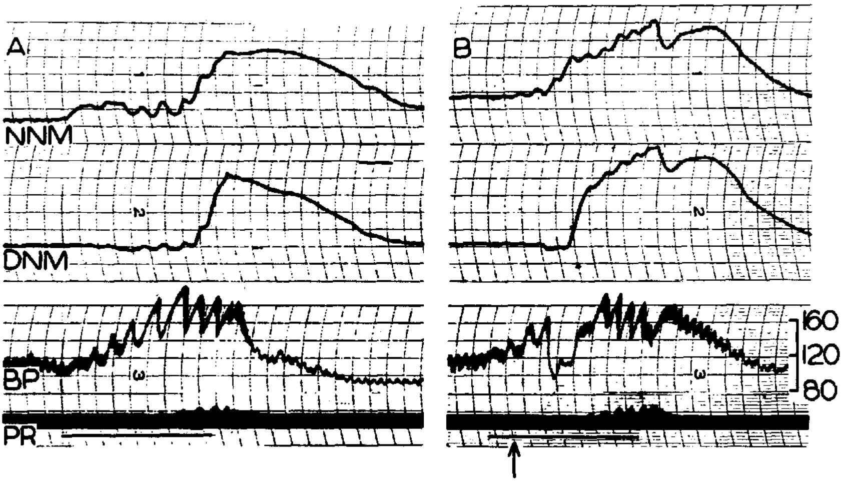

*Figure 34.* The effect of acetylcholine during asphyxia. Note the shortening of the latent period of the sympathetico-adrenal response as indicated by the onset of the contraction of the nictitating membranes.

Chloralose 85 mg/Kg and urethane 500 mg/Kg. *A*. 50 seconds asphyxia. *B*. 50 seconds of asphyxia in combination with 5 gammas of acetylcholine i.v. (injection indicated by the arrow) given during the rise of the blood pressure.

tory drugs into the posterior hypothalamus or by application of near-threshold stimuli to this structure.

Whereas the preceding records have presented evidence for an increased reactivity of the sympathetic centers in asphyxia, Figure 34 shows that this increased reactivity includes the associated endocrine functions of the adrenal medulla. It is well known that asphyxia leads to sympathetic and also to adrenomedullary discharges. In this experiment asphyxia produced a sympathetico-adrenal discharge, as indicated by the contraction of the normal *and* denervated nictitating membranes (*A*). When during asphyxia acetylcholine was injected, reflexly exciting the centers of the sympathetico-adrenal system (if given alone it did not elicit a contraction of any of the nictitating membranes), it greatly reduced the latent period of these contractions, i.e., it accelerated the sympathetico-adrenal discharges and apparently increased their duration, as suggested by the increased duration of these contractions (*B*).

Finally, the testing of parasympathetic reflexes through noradren-

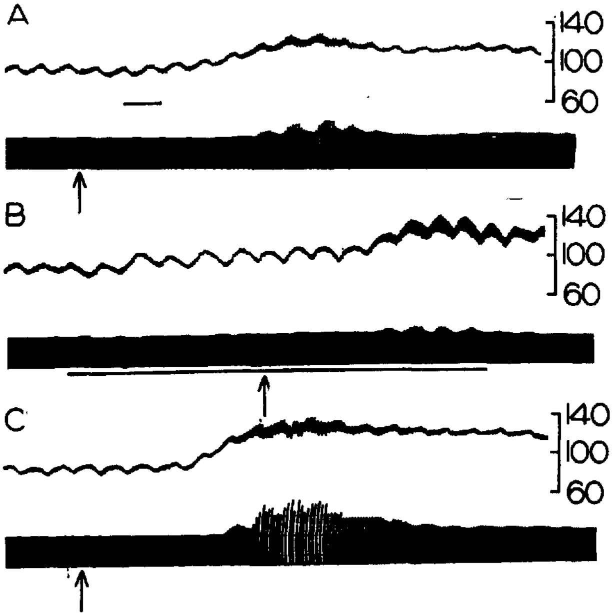

*Figure 35.* The effect of noradrenaline-induced reflex slowing during asphyxia (injection indicated by the arrow). The noradrenaline-induced reflex slowing is less in asphyxia (*B*) than in the control test (*A*) in spite of a greater rise of the blood pressure in *B*.

*A*. 10 gammas of noradrenaline i.v. *B*. 10 gammas of noradrenaline i.v. at 30 seconds during a 65-second period of asphyxia. *C*. 15 gammas of noradrenaline i.v.

aline (Fig. 35) showed that parasympathetic reactivity is diminished in asphyxia. As stated previously, the noradrenaline-induced slowing of the heart rate increases with the rise of the blood pressure. Since during asphyxia the blood pressure rise in response to a given dose of noradrenaline was greater (Fig. 35*B*) than in the control test (Fig. 35*A*), one would expect a greater reflex slowing of the heart rate if no change in the excitability of the parasympathetic centers had occurred. Actually the slowing of the pulse rate was less than in the control, a proof *a fortiori* that the excitability of the parasympathetic centers is diminished in asphyxia. The magnitude of this change is suggested by the test shown in Figure 35, in which a slightly higher dose of noradrenaline (15 gammas) was injected under control conditions in order to match the pressor effect produced by 10 gammas during asphyxia. The reduction in the pulse slowing seen in *B* as compared with *C* of this figure is an approximate measure of the diminished parasympathetic excitability in asphyxia, which in turn is intimately related to the increased excitability of the central structures of the sympathetico-adrenal system.

*(2) The modifying action of the baroreceptors in asphyxia.* Asphyxia elicits at first a rise of the blood pressure; later, however, the blood pressure falls and the pulse rate decreases. Since such variations in the blood pressure cause corresponding changes in the discharges from the sino-aortic baroreceptors, asphyxia enables one to investigate the modifying action of baroreceptor discharges on autonomic functions when these functions are also altered by changes in the internal environment.

First, the modifying action of the increased blood pressure may be considered. Hypothalamic stimulation during asphyxia (Fig. 36*B*, *D*) produced a greatly increased pressor response but, at the same time, a smaller contraction of the nictitating membrane than in the control tests (*A*, *C*). The former effect is owing to the state of sympathetic tuning in asphyxia, whereas the latter is caused by baroreceptor reflexes that are due to the greatly increased blood pressure.

It was shown earlier that when acetylcholine is applied during the initial phase of asphyxia, the sympathetic discharges are increased considerably and account for the quicker return of the blood pressure, the larger contraction of the nictitating membrane, and the more marked acceleration of the heart rate than are seen under control conditions. The mechanism involved appeared to be the summation of (a) those sympathetic impulses resulting from the hypotensive action of the drug through the corresponding alteration of the baroreceptor reflexes of the sino-aortic area, and (b) those resulting from the

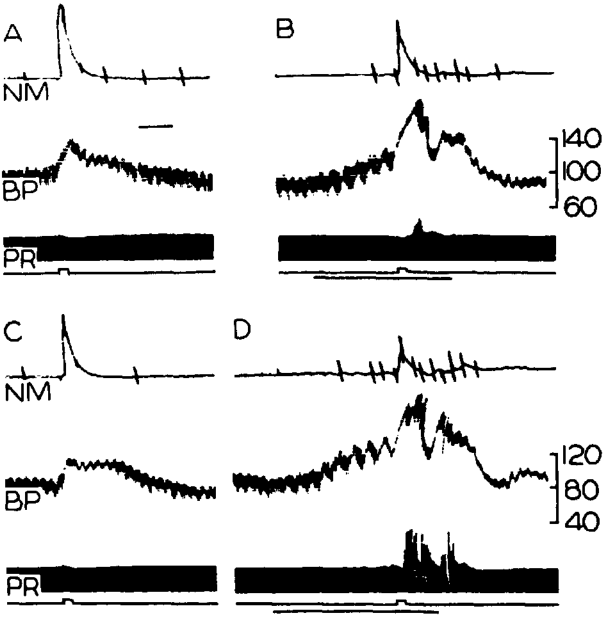

*Figure 36.* Hypothalamic stimulation in asphyxia. Note that the contraction of the nictitating membrane is partially inhibited when the hypothalamus is stimulated in asphyxia.

Chloralose 70 mg/Kg i.v. *A*. Right posterior hypothalamic stimulation (S.W.D., 1.5 v., 99 pps, 1.6 ms. for 3 seconds). *B*. 45 seconds of asphyxia with right posterior hypothalamic stimulation as in *A* after 25 seconds. *C*. Same as *A*. *D*. 50 seconds of asphyxia in combination with right posterior hypothalamic stimulation as in *C* after 35 seconds.

asphyxia, which caused excitation of the sympathetic system directly and reflexly via the chemoreceptors. This interpretation is supported by the action of acetylcholine during asphyxia when the baroreceptors are eliminated. *A*, *B*, and *C* of Figure 37 show the action of mecholyl under control conditions and during asphyxia in a normal cat. The improved return of the blood pressure from the acetylcholine-induced hypotension during asphyxia is obvious. On the other hand, after sinoaortic denervation (*D*, *E*, and *F*), it is seen that the blood pressure curve reflects only the additive effects of acetylcholine and asphyxia. Apparently, sympathetic effects cannot be elicited any longer in this experiment through hypotensive drugs after the baroreceptors have been eliminated.

*(3) The direct action of asphyxia on autonomic centers.* Our experiments have shown that during asphyxia the responsiveness of sym-

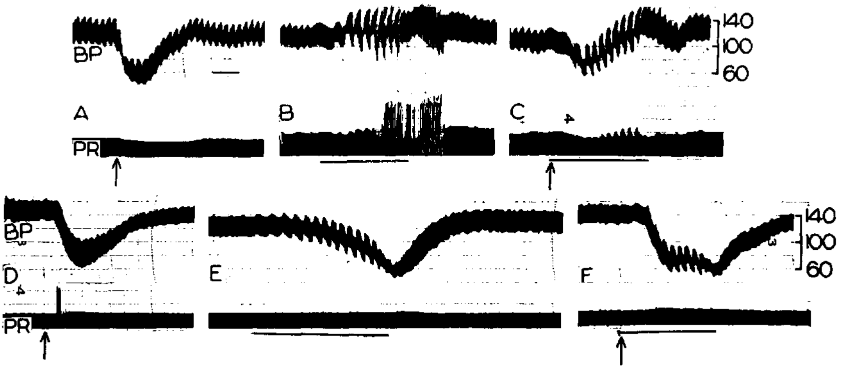

*Figure 37.* The action of mecholyl in asphyxia before (*A* to *C*) and after (*D* to *F*) denervation of the sino-aortic area. Whereas the hypotensive action of mecholyl is reduced considerably during asphyxia in the normal animal, it is aggravated after the baroreceptors have been eliminated.

*A.* 8 gammas of mecholyl i.v. *B.* 40 seconds of asphyxia. *C.* Mecholyl (8 gammas) during 40 seconds of asphyxia. *D.* 8 gammas of mecholyl. *E.* 60 seconds of asphyxia. *F.* Mecholyl (8 gammas) during 40 seconds of asphyxia.

pathetic central structures to direct and reflex stimulation is increased. Since the change in the oxygen and carbon dioxide tensions of the blood acts on the sino-aortic chemoreceptors and also on the brain itself, it is of importance to determine whether this alteration in autonomic reactivity is present after sino-aortic denervation. Figure 38 shows that in a sino-aortic denervated cat the response of the nictitating membrane to the hypothalamic stimulus is greater in asphyxia than under control conditions. The slow contraction of the nictitating membrane (particularly in the test shown at *D*) suggests that a sympathetic discharge is initiated in asphyxia through the direct action of the changes in the blood gases on the autonomic central structures. These experiments are in agreement with earlier work (124) showing that sympathetic vascular effects occur in asphyxia but not in anoxia after sino-aortic denervation and that local asphyxia of the medulla oblongata leads to a sympathetic discharge in the intact as well as in the sino-aortic denervated animal (325).

*(4) Autonomic reactivity in the postasphyxial state.* Recent observations have shown that there is a sympathetic or sympathetico-adrenal discharge not only during asphyxia but also, particularly after a prolonged asphyxia, on readmission of air. This discharge often leads to a sharp rise of the blood pressure, a contraction of the nictitating membrane, and an acceleration of the heart rate. But even in the absence of such symptoms the responsiveness of the hypothalamus to

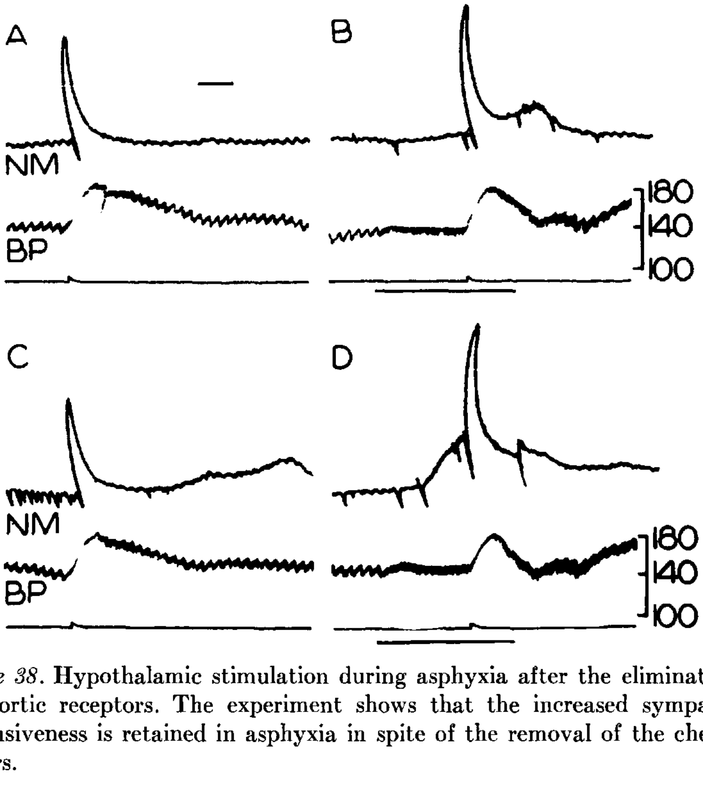

*Figure 38.* Hypothalamic stimulation during asphyxia after the elimination of sino-aortic receptors. The experiment shows that the increased sympathetic responsiveness is retained in asphyxia in spite of the removal of the chemoreceptors.

Chloralose 65 mg/Kg i.v. *A.* Right posterior hypothalamic stimulation (S.W.D., 0.6 v., 99 pps, 0.8 ms. for 0.5 seconds). *B.* 40 seconds of asphyxia in combination with right posterior hypothalamic stimulation as in *A* after 25 seconds. *C.* Same as *A.* *D.* Same as *B.*

electrical stimulation is increased at this time. Thus Figure 39 shows a much greater responsiveness of the nictitating membrane to hypothalamic stimulation in the immediate postasphyxial period than in the preceding and following control period.

Figure 39 also shows another typical postasphyxial change: the blood pressure remains elevated for some time, during which period the pulse rate is clearly diminished. This phenomenon occurs rather regularly after a prolonged asphyxia even without the intervention of a hypothalamic stimulus. If the experiment is repeated after a bilateral vagotomy has been performed, the blood pressure rises and remains elevated for some time, as in the intact animal, but the pulse slowing is absent. In its stead one notes that the pulse rate increases as the blood pressure rises above the control level and remains elevated throughout the pressor phase. The blood pressure and pulse rate return thereafter to the basic level.

From these observations it may be concluded that after prolonged asphyxia the readmission of air leads to a sympathetic discharge which persists as long as the blood pressure remains elevated. In animals

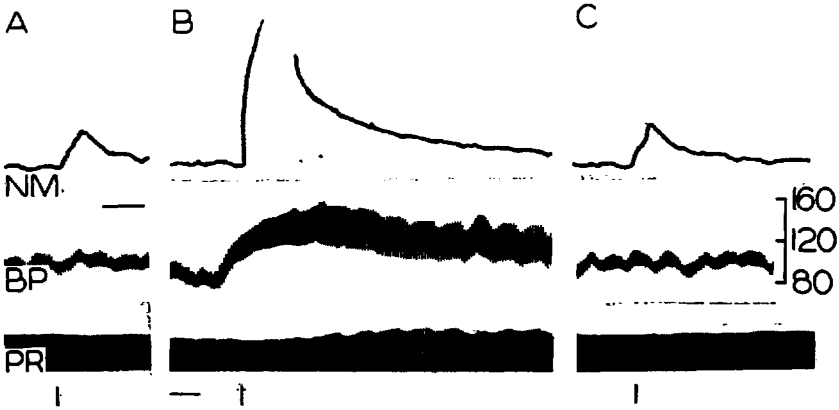

*Figure 39.* The reactivity of the hypothalamus in the postasphyxial period. The responsiveness of the sympathetic system is greatly increased immediately following the readmission of air.

*A*. Hypothalamic stimulation (2 v., 85 pps, 1.6 ms. for 3 seconds). *B*. Hypothalamic stimulation 13 seconds after the end of an 85-second period of asphyxia (the end of that period is indicated by the horizontal line at the bottom of *B*). *C*. Same as *A*.

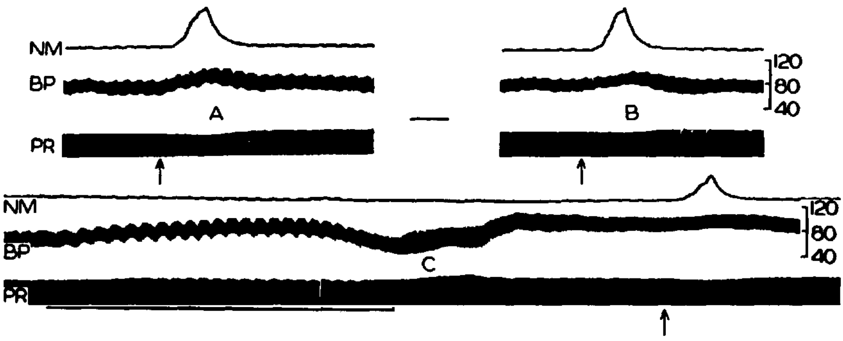

*Figure 40.* Hypothalamic reactivity in the postasphyxial state. Following a prolonged asphyxia the blood pressure remains elevated for some time during which the pulse rate shows reflex slowing and the sympathetic reactivity (see nictitating membrane in *C*) is diminished.

*A*. Stimulation of the hypothalamus (1.5 v., 51 pps, 0.8 ms. for 10 sec.). *B*. Same as *A*. *C*. Hypothalamic stimulation for 10 seconds after a 75-second period of asphyxia. (The experiments were performed in the sequence *A*, *C*, *B*.)

with intact vagi a reflex (parasympathetic) effect covers up this persistent sympathetic action on the pulse rate.

If in a normal animal (vagi intact) during this "late" postasphyxial state of parasympathetic dominance (suggested by the slowing of the heart rate) the hypothalamus is stimulated, the sympathetic responsiveness is definitely diminished. This diminution appears in the degree of the contraction of the nictitating membrane, which is less in the postasphyxial state (shown in Figure 40*C*) than in the two control periods (*A*, *B*). The pressor effect and the acceleration of the pulse rate induced by the hypothalamic stimulus in the first control period (*A*) are greatly reduced after asphyxia (*C*) and only partially restored in the second control experiment (*B*).

The experiments show that two phases of autonomic changes follow a prolonged period of asphyxia. Immediately after the readmission of air sympathetic discharges increase. During this phase the sympathetic responsiveness to central stimuli is augmented. Hereafter a second phase occurs in which in spite of persistent sympathetic discharges the parasympathetic system is called into action. During this phase of parasympathetic dominance the reactivity of the sympathetic system to centrally acting stimuli is diminished.

## C. INTERPRETATION

### 1. The Laws of Summation, Limiting Mechanisms, and the Dominance of the Sympathetic System

In the experiments described in the preceding section we at first investigated summation processes occurring within the sympathetic and the parasympathetic systems. The excitation produced by two stimuli applied in combination was found to be greater than corresponds to an algebraic summation. Thus spatial and temporal summation and potentiation were demonstrated for the sympathetic and parasympathetic nervous systems.*

The cellular mechanism underlying summation processes in autonomic ganglia has been greatly clarified through the analysis of single action potential studies. Bronk and his collaborators (33, 209) showed that under conditions involving spatial summation the rate of discharge of an individual neuron and also the number of discharging neurons increase. It is likely that similar processes occur in central autonomic structures and account for the phenomena of summation described in this monograph. From Bach's work (293), it may be surmised that the state of activity of the facilitatory system of Magoun in the reticular substance of the brain stem may also have an important influence on summation processes which involve the excitation of the hypothalamus and the medulla oblongata.

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* The following observation of Heymans (154) seems to the writer to be based on summation processes within the autonomic nervous system, although no such interpretation was given by the author. If the blood pressure in the body of dog B, whose head is perfused by dog A, is kept at different pressure levels (through bleeding and infusion), an adrenaline-induced hypertension in dog A and thereby also in the head of dog B becomes the more effective in producing vagal slowing the higher the blood pressure is in the body of dog B. This experiment seems to show that impulses from the aortic arch summate with those of the carotid sinus in dog B.

The relatively fleeting effect which a (conditioning) stimulus leaves on the somatic nervous system, as indicated by the effect of a test stimulus applied after various intervals, led Creed *et al.* (48) to assume that the stimulus produces in the central nervous system an excitatory state which decays in a short time (measured in milliseconds). The temporal facilitation occurring over relatively long intervals suggests that the central excitatory state decays more slowly in autonomic than in somatic neurons.*

There are important limiting mechanisms which influence autonomic summation processes. Thus it was seen that when a hypothalamic sympathetic stimulus was applied at the height of a pressor effect elicited by another hypothalamic stimulus, the second stimulus failed to elicit a pressor effect during the stimulation period, whereas the same stimulus under control conditions called forth a marked pressor effect. The development of a neurogenic (and, possibly, hypothalamic) hypertension which, as many authors assume, plays an important role, at least initially, in the development of clinical hypertension, would hardly be possible if the pressure-reducing mechanisms were highly effective. Our experiments show that these mechanisms exert a profound effect only when the blood pressure rises excessively; they seem to fail to prevent the development of a considerable acute rise of the blood pressure under conditions of hypothalamic stimulation (see, for instance, Fig. 23*B*, *C*), or of chronic hypertension resulting from a repeated stimulation of the medulla oblongata (292).

In this connection it is of interest to consider more closely the apparently banal fact that stimulation of the posterior hypothalamus leads to the classic sympathetic effects (rise of the blood pressure, acceleration of the pulse rate, and contraction of the nictitating membrane), frequently illustrated in our figures. Knowing that a marked pressor effect must elicit, through sino-aortic receptors, parasympathetic reflexes which would lead to a slowing of the heart rate, one would expect a hypothalamic stimulus, which causes a considerable rise of the blood pressure, to produce a slowing of the heart rate at the same time. But it is a common experience, particularly well illustrated in experiments in which the influence of increasing durations of stimulation (Fig. 2) was studied, that during this stimulation parasympathetic reflexes are completely masked. The persistence of the increased heart rate in these experiments in spite of the marked pressor effects is by no means just a special case confined to the heart reflexes, but is of general importance. It illustrates the important fact that in the normal organism the sympathetic system dominates under conditions which lead to an excitation of both divisions of the autonomic nervous system.* Such a dominance has also been seen when both divisions of the autonomic nervous system were simultaneously excited centrally or reflexly. Thus, anoxia, cold, and electrically induced convulsions, certain drugs (cocaine, bulbocapnine, metrazol†) and typhoid-paratyphoid vaccine, which produces fever, cause in the normal animal a rise, and after adreno-demedullation a fall, of the blood sugar. The rise is caused by a sympathetico-adrenal discharge which outweighs the effect of the above-named influences on the vago-insulin system. Their action on this system is shown by the fall of the blood sugar seen in adreno-demedullated animals subjected to the same experimental conditions (65–67, 98, 106, 111, 112, 120). Only increased environmental temperature causes a greater vago-insulin discharge than sympathetico-adrenal discharge in the rat.

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* The well-known fact that the positive and negative after-potentials are slower in autonomic than in somatic neurons supports this conclusion (61). Moreover, Larrabee and Bronk (209) showed that even a brief excitation of the stellate ganglion considerably increases its responsiveness to afferent impulses for several minutes!

It follows from these facts that the dominance of the sympathetic system is an important characteristic of the organization of the autonomic nervous system in the mammalian organism.‡ Limiting mechanisms exist also for the sympathetico-adrenal discharge on the blood sugar, since an increased blood sugar evokes a vago-insulin discharge via the diencephalon (330). But here again it appears that this mechanism does not prevent the sympathetic system from remaining dominant in a series of external and internal stresses, including emotional excitement ** (106), which call forth sympathetico-adrenal and vago-insulin discharges.

* This is in contrast to the parasympathetic dominance which results from severe anoxia, prolonged asphyxia, circulatory shock, etc. (see item 87, p. 152).

† Metrazol exerts sympathetic and parasympathetic effects on the cardiovascular system (108).

‡ It is not assumed that this state of sympathetic dominance prevails in all organ systems. (See Chapter 5.)

** This dominance is lost in certain psychotic conditions (113).

## 2. THE TUNING OF THE AUTONOMIC NERVOUS SYSTEM THROUGH BARORECEPTOR REFLEXES FROM THE SINO-AORTIC AREA

It was assumed that a drug-induced hypotension would evoke a state of increased sympathetic discharges via sino-aortic baroreceptor reflexes, and that a drug-induced hypertension would lead to increased parasympathetic discharges through the same mechanism. That a fall of the blood pressure (and consequently a lower pressure in the carotid sinus and in the arch of the aorta) leads to increased sympathetico-adrenal discharges, and that a rise of the blood pressure causes increased parasympathetic discharges, have been well established through the classical investigations of Hering (146), Koch (196), Heymans (154, 155), and many others. Evidence that hypotensive drugs cause a shift in the autonomic balance to the sympathetic side was found in the occurrence of a faster pulse rate and in a contraction of the normal nictitating membrane or even of the denervated nictitating membrane in very sensitive preparations; these effects indicate a sympathetic or sympathetico-adrenal discharge. Haney (138, 139, 326) has also found signs of sympathetic excitation during acetylcholine hypotension. Contrariwise, during the rise of the blood pressure caused by the injection of noradrenaline and also during the hypertensive phase following the hypotensive action of histamine, the pulse rate was slowed, an effect indicating a parasympathetic dominance.

If under these conditions the excitability of the autonomic nervous system was determined, it was found that the hypotensive state was associated with an increased responsiveness to hypothalamic sympathetic stimuli and that the hypertensive state was associated with an augmented reaction to parasympathetic stimuli. This result is obviously related to the fact that hypotension and hypertension call forth increased sympathetic and parasympathetic reflex discharges respectively as the result of diminished and augmented discharges from the sino-aortic baroreceptors.

In an attempt to explain these findings, we turn to the study of summation processes in the autonomic nervous system and the simple rules that guide them. The applicability of the rules to the state of tuning induced by baroreceptor discharges, i.e., to a state of reflexly induced autonomic imbalance, is obvious. Just as the excitatory processes summate that are evoked by two parasympathetic stimuli of hypothalamic origin or that result from the interaction of a parasympathetic hypothalamic stimulus and a parasympathetically acting sciatic reflex stimulus, so the parasympathetically increased discharges that result from a noradrenaline-induced rise of the blood pressure summate with a central (hypothalamic) or reflex (sciatic) parasympathetic stimulus. And a similar statement applies to the sympathetic summation involving a sympathetic central stimulus and a drug-induced hypotension in which sympathetic impulses are reflexly increased (through release from the inhibitory action of the baroreceptor reflexes).

Under conditions of summation, as described previously, and also in "tuning," subthreshold stimuli are highly effective. Thus distinct "tuning" effects may occur, for instance, on the heart rate, although the tuning stimulus by itself does not alter the heart rate significantly. *It may, therefore, be said that in the states of autonomic imbalance described as sympathetic or parasympathetic "tuning," the responsiveness of the autonomic nervous system is shifted respectively to the sympathetic or to the parasympathetic side as the result of sino-aortic reflexes of subthreshold or suprathreshold intensity.*

In states of autonomic imbalance, the principle of reciprocal innervation remains valid. Sympathetic tuning means not only an increased responsiveness of the sympathetic system but also a decreased responsiveness of the parasympathetic system. Similarly, the state of parasympathetic tuning reduces the effectiveness of sympathetic stimuli. It should be mentioned that a rise of the pressure of the carotid sinus by distension or by the injection of adrenaline caused an inhibition of the sympathetic impulses occurring spontaneously in the inferior cardiac nerve (31). Moreover, and this is a clear indication of a lessened sympathetic responsiveness during the adrenaline-increased phase of increased blood pressure, it was found that stimulation of the hypothalamus failed to initiate efferent sympathetic impulses during this phase.

The validity of the principle of reciprocal innervation in states of autonomic imbalance has an important consequence. It determines that a certain organ is either more susceptible to sympathetic stimuli —and then a state of sympathetic tuning* is said to exist with respect to that particular organ—or to parasympathetic stimuli—a state of parasympathetic tuning; but an increase in sensitivity to stimuli affecting both divisions of the autonomic nervous system does not occur under these well-defined conditions of physiological "tuning." The basis for this statement appears in an experiment in which the tuning of the autonomic nervous system was altered through changes in the blood pressure induced by the injection of histamine. As was described earlier, a sympathetic test stimulus, such as an electrical shock applied to a certain sympathetically acting focus in the posterior hypothalamus, elicited a greater sympathetic effect during the hypotensive phase. When the stimulus was applied at several points, as indicated in the diagram of Figure 41, the effect, as compared with that seen under control conditions, indicates that the sympathetic tuning decreased as the blood pressure recovered (*2* to *4*).* Only when a certain degree of overshooting of the blood pressure had taken place (*5*), did the sympathetic responsiveness fall below the control value, and this is the point where the parasympathetic responsiveness was augmented.

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* This state of tuning is, of course, of central origin originating (in the previously described experiments) in alterations of sino-aortic reflexes.

*On the basis of experimental data of this kind (i.e., under conditions of reflex tuning), it is suggested that not even under the crucial condition prevailing when a state of sympathetic imbalance and dominance passes over into a state of parasympathetic imbalance and dominance is there a state when sympathetic and parasympathetic responsiveness are increased at the same time.*

There are still further observations that require some comment. At point *4* of Figure 41, it was seen, sympathetic responsiveness was still increased, although it might be thought that owing to the elevated blood pressure (and therefore the increased sino-aortic pressure) the intensity of the parasympathetic sino-aortic reflexes should have been

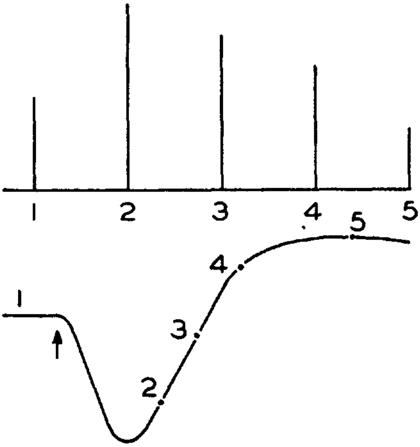

*Figure 41.* Diagram of the sympathetic responsiveness during the hypotensive and hypertensive phases which occur after intravenous injection of acetylcholine, mecholyl, and histamine. The lower curve shows the blood pressure, whereas the upper graph indicates by the height of the ordinate the changes in sympathetic reactivity.

* But the sympathetic responsiveness is still above the control value seen at *1*!

above the control level. However, such an interpretation would take too static a view of the problem of autonomic balance. The finding that at point *4* there is still a state of sympathetic tuning in spite of the fact that the blood pressure is above the control level shows that the state of sympathetic tuning does not coincide with the duration of the hypotension, but persists longer. One might express this phenomenon also by stating that there is a critical level of the sino-aortic pressure at which the autonomic centers are in a state of balance. Above this level a state of imbalance with dominance of the parasympathetic system exists, whereas below this level the sympathetic system dominates. *However, this level is not fixed, but depends on numerous circumstances.* The diagram of Figure 41 suggests that antecedent stimuli have a profound effect on this critical level as they shift the balance to the sympathetic side. Under these conditions, possibly as the result of an after-effect of the antecedent stimulus, the range of the blood pressure within which the sympathetic dominance occurs is widened by the inclusion of relatively high blood pressure levels (as at point *4* of the diagram).

On the other hand, changes in the critical level of the blood pressure, which determines whether autonomic balance or imbalance shall prevail at a given blood pressure, may occur also after a marked shift in the autonomic balance to the parasympathetic side. However, there are fundamental differences between the two cases. First, there is no good evidence that parasympathetic tuning—for instance, that induced by the injection of noradrenaline—persists beyond the hypertensive period. As a matter of fact, it seems that parasympathetic tuning is mostly confined to the phase when the pressor effect is greatest. Hereafter, as the blood pressure falls to the control level or slightly below it, an increased responsiveness of the sympathetic nervous system occurs (see Fig. 11) which is greater than that expected from the change in the blood pressure. Apparently, in spite of different mechanisms involved in the two cases, there is a tendency to increased sympathetic responsiveness following sympathetic and parasympathetic reflex tuning before the ultimate balance is reached. In view of the fact that physiologically the sympathetic system is dominant, as the blood sugar experiments discussed earlier indicate,* these peculiar reactions may be looked upon as safeguards to maintain the normal state of autonomic balance after it has been altered experimentally (and possibly clinically).

Although the tuning is specifically restricted to either the sympathetic or the parasympathetic division of the autonomic nervous system, the action of the reciprocally inhibited autonomic discharges is not lost. *They codetermine the degree of tuning of the dominant branch of the autonomic system.* This is the reason why at a similar degree of elevation of the blood pressure the parasympathetic responsiveness is much greater when it results from the injection of noradrenaline than when it results from the overshooting which follows a histamine-induced hypotension. In the second case the development of the parasympathetic dominance is opposed by the after-effect of the preceding condition of sympathetic dominance.* This after-effect accounts not only for a shift in the critical sino-aortic pressure level, which determines whether the autonomic centers are in a state of balance or not, but also for the continuance of a relatively high rate of sympathetic discharge, still present when finally parasympathetic dominance has been achieved. Because of the persistence of these sympathetic discharges into the state of histamine-induced parasympathetic dominance, the parasympathetic responsiveness is less in this case than in the analogous case of noradrenaline-induced dominance, in which the sympathetic impulses are inhibited and discharge at a rate below the control level.

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* The sympathetic dominance is a function of age, being greatest in very young animals (269).

There are analogies for some of these findings in the investigations of Sherrington on the somatic nervous system. If a flexor reflex is evoked by the stimulation of an ipsilateral nerve and an extensor reflex by stimulation of a contralateral nerve, the simultaneous administration of both stimuli does not result in an activation of flexor and extensor muscles but in the dominance of one of them (usually of the flexor muscles) with reciprocal inhibition of the antagonists.

Sherrington evoked the utility principle for an understanding of this phenomenon, since a mixed action involving both antagonistic muscles or muscle groups would be an inadequate response to either stimulus. This argument seems to be equally valid for the autonomic tuning process. A dominance of the parasympathetic system would serve restitutional processes such as were obtained by Hess (151) in his studies on anterior hypothalamic functions; a dominance of the sympathetic system would prepare the organism better for fight and flight, but a state of increased responsiveness of both systems would serve no physiological purpose. This does not mean that such a state may not occur as the result of pathological processes involving the centers of the autonomic nervous system.†

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* See the discussion of Figure 16.

† This discussion seems to be valid only for those parasympathetic and sympathetic processes which act on the same organ. If the organism as a whole is considered, sym-

## 3. FURTHER CHARACTERISTICS OF THE TUNING PROCESS

For investigative as well as descriptive purposes some simplifying assumptions are often necessary in order to establish certain basic concepts and make their experimental verification possible. These concepts may then be modified and supplemented in the light of further studies and of a more searching analysis. In the problem under discussion it must now be determined, whether the concept of sympathetic (or parasympathetic) tuning characterized by an increased sympathetic (or parasympathetic) responsiveness and a reciprocally diminished responsiveness of the parasympathetic (or sympathetic) system reflects adequately the variety of the experimental data and the complexity of the regulating mechanisms of the autonomic nervous system.

The experimental data show that the effect of sympathetic or parasympathetic tuning is not uniform on the various structures and functions investigated in the present study. The influence of sympathetic tuning, for instance, when tested with a sympathetic hypothalamic stimulus, may in one experiment appear as an increased responsiveness of the blood pressure, pulse rate, and contraction of the nictitating membrane, and in another may be confined to one or two of the three indicators. Or the tuning may, in addition, lead to a contraction of the denervated nictitating membrane (indicative of adrenomedullary secretion) on application of the test stimulus, an effect which was absent under control conditions. Bearing in mind that the action of tuning was investigated on but a few indicators, it may be suggested that if the number of organs and functions studied were multiplied, an even greater variety of gradations in the action of tuning would be revealed than was shown in the present experiments. But even on the basis of our limited material it is certain that the tuning may influence small or large parts of either division of the autonomic nervous system. In the first case we may speak of partial sympathetic or parasympathetic tuning.

It has long been recognized that the parasympathetic system may be activated partially, but Cannon's work has led many to believe that the sympathetico-adrenal system always discharges as a whole.

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pathetic and parasympathetic discharges may occur at the same time as in conditions of stress. Then, as the result of central autonomic discharges, the vago-insulin *and* the sympathetico-adrenal systems are activated. Owing to the dominance of the sympathetico-adrenal discharges an increase in the blood sugar occurs, but it is accompanied by an increase in the concentration of insulin in the blood. Under these conditions the utilization of glucose is greatly increased (see item 94, pp. 334ff). In other words, in spite of the discharge of both divisions of the autonomic system a highly purposeful action is accomplished.

Earlier work (107) showed that under conditions of central stimulation of cerebral and spinal structures, partial sympathetic discharges can easily be demonstrated. The occurrence of a partial tuning appears to be related to this type of central discharges.

In addition, it should be borne in mind that the effect of tuning as it appears on a particular organ depends on the number of impulses, synergistic and antagonistic to the "tuning stimulus," that impinge on this organ at the same time. This must be so since the effect of tuning, as we have seen earlier, is based on processes of summation and potentiation. Consequently, the degree of tuning — induced, for instance, by a fall in the sino-aortic pressure — may vary widely in different organs, depending on the type and intensity of the segmental reflexes that influence them at the same time.

But we have to go still further. Even under the relatively simplified conditions of the analytical experiment it could be shown that the dominance of one division of the autonomic system due to tuning does not go unchallenged. Figure 13 illustrates an experiment in which during the state of hypothalamically induced sympathetic tuning, noradrenaline was used as a test stimulus. In addition to the expected diminished parasympathetic reflex responsiveness (measured by the noradrenaline-induced slowing of the heart rate), it was noted that the injection of noradrenaline inhibited the contraction of the nictitating membrane produced by the sympathetic "tuning" stimulus. This inhibition is obviously due to a sino-aortic reflex resulting from the elevation of the blood pressure induced by noradrenaline.* The experiment illustrates the fundamental fact that during the administration of the parasympathetic test stimulus (noradrenaline) the previously evoked state of sympathetic tuning may persist in one organ (heart) and be inhibited in another organ (nictitating membrane). Since the inhibition of the sympathetic impulses in an organ is accompanied by the establishment of a parasympathetic dominance (provided that the organ is supplied by nerves from both divisions of the autonomic nervous system) we come to this conclusion: *as the result of the central interaction of parasympathetic and sympathetic stimuli a state of sympathetic tuning may occur in one group of organs and structures while a parasympathetic state of tuning exists in other parts of the body.*†

## 4. The Physiological Basis of the Reversal Phenomenon

The fundamental functional alteration that may result from "tuning" is most dramatically illustrated by the "reversal" phenomenon.

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* See Figure 22.

† See Chapter 5.

This is the phenomenon that occurs when a stimulus previously productive of a sympathetic effect calls forth, under the new condition, a parasympathetic action (reversal). Similar reversal phenomena have been noted in experiments involving peripheral stimulation of the autonomic nerves. Hess (152) rightly calls attention to the fact that, although on electrical stimulation of a nerve all nerve fibers may be activated, only the action of the dominant group determines the functional effect. Thus electrical stimulation of the vagus elicits a slowing of the heart rate; nevertheless the presence of accelerator fibers in this nerve is well established (189). In exercise these fibers are selectively activated (34). Variations in the frequency of vagal stimulation produce a relaxation or a contraction of the fundus of the stomach (236, 237).

The reversal in the reactivity of the uterus of the cat in the virginal as compared to the nonvirginal state is well established (49); and Kolm and Pick (202, 203) have shown that after pretreatment with acetylcholine or muscarine the heart, blood vessels, and gastrointestinal tract show in response to adrenaline a vagotropic response. Similarly, they observed that in a calcium-free medium adrenaline exerts a vagus-like action on the heart. The findings that stimulation of the lumbosacral plexus causes a vasodilatation in the hindlegs of the frog during perfusion with adrenaline, but a vasoconstriction under control conditions (15), and the demonstration of the reversal of the blood pressure effect of adrenaline after the administration of ergot preparations (50), are further examples of reversal phenomena under the influence of drugs.

The application of these data to conditions of *central* excitation of the autonomic nervous system and the reversal phenomenon is amply justified by two facts: (a) that from the same focus in the hypothalamus sympathetic or parasympathetic effects may be elicited by lowering the frequency of the stimulation (140, 148); (b) that in our own experience sympathetic and parasympathetic effects are frequently mixed on stimulation of the hypothalamus (107). On the basis of these data it may be assumed that reversal is due to a shift of the autonomic balance. A stimulus which activates parasympathetically and sympathetically acting neurons, with the latter predominating under control conditions, will, as the result of a reflexly induced parasympathetic tuning, display only parasympathetic effects.*

This interpretation is well supported by the type of experiment illustrated in Figure 19, in which the hypothalamic test stimulus elicited under control conditions a biphasic effect: first, a slight fall in the blood pressure (parasympathetic), later a rise in the blood pressure and pulse rate (sympathetic). At the height of parasympathetic tuning induced by noradrenaline the first effect was greatly aggravated and the second was almost abolished. We are dealing here, it seems, with a situation intermediate between the ordinary tuning effects and the reversal phenomenon, since in spite of the distinguishable biphasic components of the stimulus effects, the pressor phase predominates under control conditions and the depressor phase during tuning.

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* Our interpretation is in agreement with that advanced by Schaefer for various heart reflexes (270, pp. 118ff).

### 5. SUCCESSIVE AUTONOMIC INDUCTION

When the sympathetic division of the hypothalamus is stimulated, the autonomic effect is not restricted to the period of stimulation. After-effects may appear in two forms: (a) as a persistence of the sympathetic discharge which develops during the period of stimulation and not infrequently shows its maximum afterward (see, for instance, Figs. 6*B* and 10*E*); (b) as a sudden change from the sympathetic to the parasympathetic type of discharge. In this case the blood pressure may fall instead of continuing to rise, and the acceleration of the heart rate may be replaced by a group of often very slow (vagal) pulses.

Systematic studies, in which parameters of stimulation were varied over a wide range, showed that this parasympathetic after-discharge, referred to as successive autonomic induction, increases with increased effectiveness of the preceding sympathetic stimulation, regardless of whether this is accomplished by increasing the voltage or stimulus frequency, by alteration of the pulse duration, or by increase of the duration of the period of stimulation.*

At least two factors may underlie this phenomenon. From experiments on prolonged stimulation of the peripheral vago-sympathetic nerve it is known that one of the component nerves stops functioning earlier than the other so that the heart rate shows two successive periods, of a parasympathetic and sympathetic character respectively. Realizing that the stimulation of the hypothalamus frequently or perhaps even invariably leads to the activation of neurons belonging to both divisions of the autonomic nervous system, a differential ability of these neurons to produce an after-discharge may play a role in successive induction. In addition, it was emphasized that parasympathetic reflex effects are suppressed during the stimulation period when the sympathetic action predominates in hypothalamic stimulation, and it may be safely assumed that the discharge from directly stimulated parasympathetic neurons will be likewise inhibited. Moreover, it is well known that activity which has been inhibited during the stimulation of antagonistic neurons, frequently appears with increased intensity after the cessation of such a stimulus (Sherrington's "rebound"). It is suggested that the phenomenon of successive autonomic induction is analogous to the "rebound" of spinal reflexes.

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* Redgate and Gellhorn (unpublished observations).

If it is true that a sympathetic discharge induced by direct electrical stimulation of the hypothalamus has a tendency to be followed by a parasympathetic phase after the cessation of the stimulus, it is not unlikely that such a "rebound" phenomenon will occur also under conditions of reflex excitation. Observations on autonomic excitability during and following a noradrenaline-induced parasympathetic tuning seem to bear out the validity of this suggestion (Fig. 11). It seems likely that a slow swing in the autonomic balance from the noradrenaline-induced phase of parasympathetic tuning to a phase of sympathetic dominance and then back to the normal level of autonomic balance is involved. This would be a similar but slower change of the autonomic balance than is seen after electrical hypothalamic stimulation.

Regardless of the mechanism which underlies these phenomena, the phase of successive autonomic induction indicates a parasympathetic discharge. This discharge may summate with other parasympathetic discharges or it may be suppressed by simultaneous sympathetic discharges. It is, therefore, *an excellent test to ascertain the state of autonomic balance.* As was to be expected, it was found that in a state of parasympathetic tuning the successive autonomic induction was augmented (Fig. 15), whereas a state of sympathetic tuning tended to suppress it (cf. Fig. 32).

### 6. SINO-AORTIC DENERVATION AND THE AUTONOMIC NERVOUS SYSTEM

It has been shown that the sympathetic tuning induced by hypotensive drug action and the parasympathetic tuning accompanying a drug-induced elevation of the blood pressure are abolished after sino-aortic denervation (see Figs. 20–22). On this basis it is suggested that the following phenomena depend likewise on baroreceptor reflexes: (a) the increased responsiveness of the sympathetic system during a reflexly or directly induced hypotension, the former resulting from a low-frequency stimulation of the sciatic nerve, the latter from a direct excitation of parasympathetic neurons of the hypothalamus; (b) the changes in autonomic excitability induced by the fall of the blood pressure level after hemorrhage and by its rise following the injection of dextran; (c) the increased sympathetic responsiveness noted during the slight fall of the blood pressure that follows the noradrenaline-induced hypertension.

It was further shown that sino-aortic reflexes set limitations upon the degree of autonomic excitation: the contraction of the nictitating membrane is reduced in the normal animal when the hypothalamic stimulus is applied at a greatly increased blood pressure (which was produced by another sympathetic hypothalamic stimulus). After elimination of the sino-aortic receptors, these fundamental changes in autonomic reactivity and balance occur no longer. Some effects, however, of changes in the blood pressure on the responsiveness of autonomically innervated organs remain. Thus some rather slight differences in the reactivity of the nictitating membrane to hypothalamic stimulation occur in sino-aortic denervated animals during drug-induced hypotension and hypertension, as compared with the reactivity of the membrane to this stimulation under control conditions, but these changes are opposite to those seen when the buffer reflexes are intact. The slight diminution in the responsiveness of the nictitating membrane during hypotension and the small increase during hypertension seem to indicate that the reactivity of autonomic hypothalamic centers, in the absence of baroreceptor reflexes, increases with increasing blood pressure, whereas in the normal organism the opposing action of the baroreceptor reflexes obscures this action of the blood pressure level per se and reverses the effect. Similar results were obtained in a study on the relation between baroreceptor activity and convulsions (129, 130). In the normal animal convulsions were intensified by hypotension and inhibited by hypertension, suggesting that convulsive activity increases with sympathetic tuning; in the sino-aortic denervated animal, changes of blood pressure had only slight effects, and these were again opposite to those seen in the normal organism.*

## 7. TUNING OF THE AUTONOMIC NERVOUS SYSTEM THROUGH A CHANGE IN THE INTERNAL ENVIRONMENT

Autonomic tuning brought about by a change in the internal environment is a potentially very large and important area of knowledge that has only been touched on in the present investigation. Earlier studies on the action of anoxia (105) and carbon dioxide (87) suggested that excitatory effects are exerted from the sino-aortic chemoreceptors on the sympathetic division of the hypothalamus. These studies need considerable extension.

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* It would be desirable to ascertain the role of the intrasinusal pressure on the tuning process directly by studying the influence of variations of pressure on one isolated carotid sinus, as in the experiments of Heymans (154) and Koch (196). In order to avoid a change in the blood pressure that in turn would influence the tuning via the other carotid sinus, a compensatory device as described by Fog (69) should be used.

It is highly probable that changes in the internal environment induced by alterations in ionic concentrations, blood sugar, blood gases, hormones, etc. influence the excitability of central structures of the autonomic nervous system partly through action on the chemoreceptors of the sino-aortic area and partly through direct action on the brain itself. In the present work the action of asphyxia was investigated because its profound effect on the sympathetico-adrenal system has long been known. As was to be expected, the sympathetic tuning occurring in asphyxia resulted in an increased responsiveness to hypothalamic sympathetic stimuli and to sympathetically acting reflex stimuli (hypotensive drugs, Figs. 33 and 34), whereas the responsiveness of the parasympathetic system, indicated by the noradrenaline-induced slowing of the heart rate and the intensity of successive parasympathetic induction following hypothalamic sympathetic stimuli, was lessened. This state of tuning was produced by asphyxia even after sino-aortic denervation, a result indicating that the change in the internal environment contributed to the tuning not only through action on the chemoreceptors but also by direct action on the brain.*

Following prolonged asphyxia, a sympathetic or sympathetico-adrenal discharge occurs when air is readmitted. Thus a state of sympathetic dominance is attained or intensified when asphyxia is produced and when it is alleviated. After a severe alteration of the internal environment, apparently even the return to physiological conditions produces profound effects on the autonomic system and also on the cerebrospinal system, as the increased tendency to convulsions (272) and the augmented sensitivity of sensory functions (128, 272) suggest.

The state of sympathetic dominance that takes place upon the readmission of air passes over into one of parasympathetic dominance, during which the blood pressure remains elevated and the pulse rate is reduced. This second phase of autonomic imbalance following reoxygenation is of considerable interest for several reasons: (a) It illustrates again the swing in the excitability of the autonomic nervous system from sympathetic dominance to parasympathetic dominance before the final equilibrium is reached. (b) It allows further insight into the state of autonomic imbalance.

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* Since the blood pressure rises in early asphyxia when a state of sympathetic tuning exists, the baroreceptors can only play a role in somewhat reducing the degree of sympathetic dominance.

When this postasphyxial state is investigated in normal and vagotomized animals, it is noted that in the normal cat the pulse rate is lower than in the preasphyxial state, whereas in the vagotomized animal it is higher. Apparently, the sympathetic discharge initiated by the reoxygenation after prolonged asphyxia in the normal animal continues to a certain degree while, as indicated by the slowing of the pulse rate, a state of parasympathetic dominance develops. Sympathetic hypothalamic stimuli applied during this stage show a definite and reversible diminution in effectiveness, as seen particularly in the size of the contraction of the nictitating membrane (see Fig. 40*C*) but also in the responses of blood pressure and pulse rate. These experiments show that even with sympathetic discharges above the control level, the responsiveness of the sympathetic system is decreased if this discharge occurs in a state of parasympathetic dominance. The principle of reciprocal innervation remains valid in the postasphyxial state. *The state of tuning does not appear to be related to the absolute degree of the rate of discharge of any division of the autonomic system, but is determined by the division that is dominant.*

CHAPTER 2

# HYPOTHALAMIC EXCITABILITY, PHASIC AUTONOMIC REFLEXES, AND TONIC AUTONOMIC FUNCTIONS

ONE goal of this work, it was pointed out in the Preface, was to understand certain clinical observations on the action of mecholyl in patients with neuropsychiatric disorders. The experimental work, to be discussed in this chapter, seems to the writer to prove his original contention that the mecholyl test, other conditions being equal, reflects the state of excitability of the sympathetic division of the hypothalamus. These observations are a challenge to establish methods by which also the state of the parasympathetic division of the hypothalamus may be determined. Such an investigation is important, since an insight into the state of autonomic balance or imbalance can be gained only by the determination of the state of excitability of the centers of *both* divisions of the autonomic nervous system. The dependence of the noradrenaline-induced slowing of the heart on the state of excitability of the parasympathetic division of the hypothalamus will be shown in this chapter. This test in conjunction with the mecholyl test should make it possible to determine the nature of the autonomic balance in the intact organism. It should also tell whether or not the reciprocal relation that characterizes the physiological state of autonomic balance and the state of imbalance induced reflexly via the sino-aortic receptors holds for the experimentally induced condition of imbalance that results from hypothalamic lesions and alterations in hypothalamic excitability.

Although the primary aim of the experiments discussed in this chapter is to establish the relation between certain autonomic tests and the excitability of the hypothalamus in the intact organism, the data thus obtained are valuable from another point of view. In the experiments to be described in this section, the reactivity of the hypothalamus and its balance were altered by various procedures involving a direct action on this structure. The hypothalamic imbalance produced thereby was analyzed experimentally in a manner similar to that employed in states of a reflexly induced autonomic imbalance ("reflex tuning"). A comparison between the two states of autonomic imbalance discloses that the reactivity of the central autonomic structures is altered similarly in the two types of imbalance. Furthermore, the laws of summation discussed earlier are applicable to these hypothalamically induced imbalances and satisfactorily explain the changes in the responsiveness to noradrenaline and mecholyl seen when the excitability of the hypothalamus is altered.

A final group of observations seems of equal physiological and clinical significance. Although the emphasis has been placed thus far on the phasic reflex changes induced by noradrenaline and by drugs of the mecholyl group, it should be added that important changes in the level of the blood pressure and in the heart rate occurred when the excitability of either division of the hypothalamus was altered chemically (by the injection of drugs) or, and this appears to be most important, through lesions placed in specific areas of the hypothalamus through high frequency currents. Since this method, first developed by Hess (147) allows one to destroy nervous tissue without any apparent signs of excitation, it disclosed a tonic influence of the hypothalamus on the blood pressure and the heart rate which was heretofore unknown.

## A. A BASIC CLINICAL OBSERVATION

In a series of papers Funkenstein, Greenblatt, and Solomon (77–82) reported the results of their administration of the mecholyl and the epinephrine tests to normal persons and to patients. The latter comprised chiefly, but not exclusively, persons with neuropsychiatric disorders. Mecholyl (10 mg.) was injected intramuscularly and epinephrine (0.05 mg.) intravenously. Thereafter the blood pressure was taken at half-minute to one-minute intervals for a period of 10 to 25 minutes. A discussion of the epinephrine tests may be omitted. They seemed to me not to result in significant changes and have been omitted in later papers of the authors. The mecholyl tests, however, yielded interesting results. Although the authors classified their results in seven groups, it seems permissible, by omitting minor differences, to distinguish three groups only. The first group is characterized by a relatively slight fall of the blood pressure, a quick return to the control level, and a subsequent marked overshooting. In the second, intermediate group, the fall of the blood pressure is slightly greater and lasts distinctly longer than in Group I. The blood pressure returns to the base line within 8 or 9 minutes, and *there is no overshooting.* Finally, Group III shows a greater degree of hypotension and a prolongation of the hypotensive action so that the control level of the blood pressure is not yet reached after 25 minutes.* The authors state that about 80 to 90 per cent of the "normals" are represented in Group II. It is, therefore, Groups I and III that show autonomic disturbances suggesting a relation to mental illness. This relation is borne out by the important observation that improvement or impairment of the clinical condition of the patient is associated with an alteration of the blood pressure reactions that are induced by mecholyl. If these reactions do not change, the clinical picture is unaltered.

These clinical observations are a challenge to the neurophysiologist who is interested in psychophysiological relations in general and in an understanding of mental disorders in terms of central nervous functions in particular. *The studies of Funkenstein et al. pose the question whether the type of blood pressure reaction induced by mecholyl is related to, or possibly a measure of, the reactivity of specific parts of the brain which play a fundamental role in mental disorders.*

Obviously, a physiological interpretation of the relation of the mecholyl reaction to the mental state of the patient must be based on an analysis of the changes in the central nervous system induced by the injection of this drug. That autonomic changes are involved is recognized by Funkenstein *et al.*, who speak of "autonomic changes paralleling psychologic changes in mentally ill patients." What is the nature of these autonomic changes? The experiments reported in the following sections have been planned to give an answer.

## B. THE DEPENDENCE OF THE ACTION OF MECHOLYL AND OTHER HYPOTENSIVE DRUGS ON THE EXCITABILITY OF THE POSTERIOR HYPOTHALAMUS

In numerous experiments it has been shown that mecholyl as well as other hypotensive drugs elicits a sympathetic discharge through the diminution of the baroreceptor reflexes that hold the activity of the sympathetico-adrenal system in check. Moreover, considerable similarity was found between the sympathetic or sympathetico-adrenal effects elicited by direct stimulation of the medulla oblongata or the hypothalamus and those occurring during a drug-induced hypotension. When on stimulation of the hypothalamus or the medulla oblongata the nictitating membranes were used as indicators, a contraction of the normal but not of the denervated nictitating membrane showed that weak stimuli led to discharges via the sympathetic nerves, and not via an adrenomedullary secretion. Stronger stimuli, however, led also to a contraction of the denervated nictitating membrane which began after a relatively long latent period. These general characteristics of a sympathetico-adrenal discharge appeared likewise when acetylcholine, mecholyl, or histamine were injected intravenously.*

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* There are some persons who show almost no change in the blood pressure after the injection of mecholyl. We have likewise seen such poor reactors. This group is not utilized in this discussion.

Although these observations show that the hypotensive action of mecholyl and similar drugs is accompanied by a sympathetic or a sympathetico-adrenal discharge, they do not prove a relation between the degree of hypotensive action and this autonomic discharge. It is the purpose of the present chapter to show: (a) that the degree of the hypotensive action of mecholyl and similar drugs is inversely related to the sympathetic discharge; (b) that the hypothalamic sympathetic centers are chiefly involved in this discharge; (c) that the hypotensive action of drugs of the mecholyl group may be used as an indicator of the excitability of the sympathetic division of the hypothalamus in the intact organism.

First, a group of experiments may be discussed that throw some light on the relation between hypotensive action and sympathetic discharge, although no attempt was made to influence the discharging centers directly. The study of the action of acetylcholine, mecholyl, and histamine revealed that in response to different doses of the drugs the sympathetico-adrenal response varied widely. Thus Figure 42 shows that in this particular instance the "neurogenic" sympathetic response, as measured by the contraction of the normal nictitating membrane, was much greater in the first than in the two subsequent tests. On the other hand the humoral response, indicated by the contraction of the denervated nictitating membrane, increased slightly from tests *1* to *3*. This fundamentally different behavior of the two indicators allows one to determine whether the neurogenic or the hormonal response is of decisive importance for the recovery of the blood pressure from the hypotensive action. The important fact illustrated by this and similar experiments is the parallelism between the "neurogenic" sympathetic discharge and the blood pressure curve. In test *1* a strong sympathetic discharge was accompanied by a rapid return of the blood pressure to the control level and a marked overshooting following the hypotensive action, whereas in tests *2* and *3* the progressive decline of the "neurogenic" discharge was associated with a progressive delay in the return of the blood pressure from the

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* Drugs such as TEA (tetraethylammoniumchloride), which are known to block autonomic discharges, abolish this activity of the nictitating membranes regardless of whether this effect stems from the stimulation of autonomic central structures or from the action of hypotensive drugs (94).

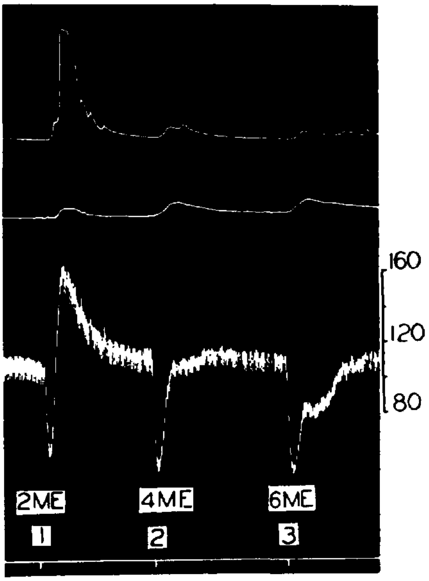

*Figure 42.* The effect of mecholyl on blood pressure and nictitating membrane. Note that the return of the blood pressure from the hypotensive action of mecholyl is determined by the sympathetic responsiveness of central autonomic structures, which is indicated by the height of contraction of the normal nictitating membrane, Gellhorn and Redgate (127).

*First line*—normal nictitating membrane. *Second line*—denervated nictitating membrane. *Third line*—blood pressure. 2, 4, and 6 gammas of mecholyl were injected i.v. at *1*, *2*, and *3*, respectively.

hypotensive action of mecholyl. Since the contraction of the denervated nictitating membrane increases from tests *1* to *3*, it may be said that *the neurogenic and not the humoral sympathetic discharge is chiefly responsible for the type of blood pressure curve which results from the injection of a given dose of mecholyl.*

In order further to investigate the relation between the activity of the autonomic centers and the hypotensive action of mecholyl and related drugs, experiments were performed in which the state of discharge was altered in these centers by three procedures: (a) the injection of drugs in minute quantities into specific areas of the hypothalamus; (b) the near-threshold stimulation of these structures with electrical currents or their excitation by means of hypercapnia; (c) the study of hypothalamic lesions induced by high frequency coagulation. In addition, advantage was taken of the effect of variations in the degree of anesthesia on autonomic centers, since under these conditions data were obtained on the relation between the intensity of the hypothalamic discharge and the action of hypotensive drugs.

### 1. The Intrahypothalamic Action of Metrazol and Strychnine*

If minute quantities (0.02 to 0.04 cc.) of a 1 per cent strychnine or 10 per cent metrazol solution are injected into the posterior hypothalamus, its responsiveness to electrical stimulation and thereby its sympathetic action on the blood pressure, nictitating membrane, and the heart rate are distinctly increased. If under these conditions acetylcholine, mecholyl, or histamine is injected, its hypotensive action is diminished and the signs of sympathetic discharge which accompany this action are augmented. This phenomenon is illustrated in Figure 43. After the injection of strychnine, the blood pressure curve shows that a lesser reduction in the pulse pressure during the hypotensive phase and more overshooting following this phase occurred than in the control test. The acceleration of the pulse was greater and more prolonged. Finally, a considerable contraction of the normal nictitating membrane occurred, whereas this membrane showed only an insignificant contraction during the acetylcholine test under control conditions. Since the denervated nictitating membrane reacted similarly before and after the injection of strychnine, it follows that in this test the injection of strychnine into the hypothalamus increased the sympathetic discharge to acetylcholine-induced hypotension. However, the adrenomedullary secretion was not increased.

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* Gellhorn and Redgate, 127.

Figures 44 and 45 show that the action not only of acetylcholine but also of mecholyl and histamine is similarly altered under the influence of a drug which increases hypothalamic excitability. Under control conditions (left section of the figures) it is seen that acetylcholine and mecholyl produce a prolonged and not quite reversible hypotension, associated with small contractions of the normal nictitating

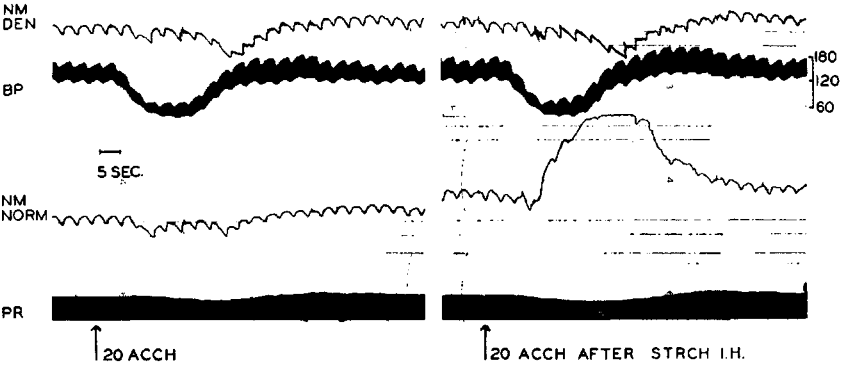

*Figure 43.* The effect of a bilateral injection of strychnine (0.04 cc., 1 per cent) into the posterior hypothalamus on the responsiveness of the blood pressure, pulse rate, innervated (NM Norm) and denervated nictitating membranes (NM Den) to 20 gammas of acetylcholine (injections indicated by the arrows). The accelerated recovery of the blood pressure, the increased pulse rate acceleration, and the increased contraction of the normal (but not of the denervated) nictitating membrane indicate augmented sympathetic responsiveness of the hypothalamus after the injection of strychnine, Gellhorn and Redgate (127).

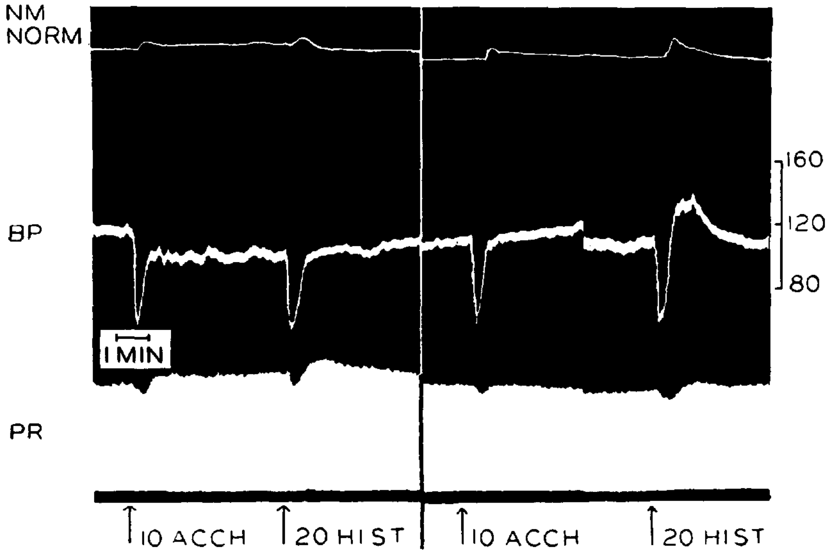

*Figure 44.* The effect of a unilateral injection of metrazol (0.04 cc., 10 per cent) into the posterior hypothalamus on the responsiveness of the blood pressure, pulse rate, and normal nictitating membrane to 10 gammas of acetylcholine and to 20 gammas of histamine (injections indicated by the arrows). Note that the sympathetic responsiveness is augmented after metrazol as indicated by the more complete recovery of the blood pressure from the acetylcholine-induced hypotension, the overshooting of the blood pressure in the histamine test, and the increased contraction of the nictitating membrane in both tests. The left section shows the tests before, the right section after metrazol, Gellhorn and Redgate (127).

membrane. After a unilateral injection of metrazol into the posterior hypothalamus (right section of the figures) the hypotensive effect is greatly shortened and completely reversible. The contractions of the nictitating membranes are approximately doubled after metrazol. Still more striking are the alterations induced by metrazol in the action of histamine. Whereas histamine produces only a hypotensive effect under control conditions, it causes, after the administration of metrazol, the appearance of a marked hypertensive phase following the initial fall of the blood pressure. The contraction of the nictitating membrane is likewise increased. The changes in the pulse rate are only slight. It seems to be characteristic that after metrazol there is less slowing of the pulse rate (particularly in the histamine test), although histamine elicits a marked secondary hypertension. That the change in the reactivity of the pulse rate is not due to a weakening of vagal reflexes is obvious from the adrenaline test. This test shows that the reflex slowing of the heart persists after the metrazol injection. It demonstrates also that the peripheral action of adrenaline on the nictitating membrane is not affected by the intrahypothalamic injection of metrazol.

In these and similar experiments an inverse relation was seen between the sympathetic excitability of the hypothalamus to electrical stimulation and the hypotensive action of mecholyl and related drugs. It may, therefore be concluded that an increased sympathetic excitability of the posterior hypothalamus produced by the injection of excitatory drugs leads to a diminution of the hypotensive phase or even to the development of a hypertensive phase ("overshooting") absent under control conditions. This change is accompanied by other signs of increased sympathetic discharges (increased acceleration of the heart rate and larger contraction of the nictitating membrane). Since with the return of the hypothalamic excitability after a certain interval of time (20 to 30 minutes) the action of the hypotensive drugs

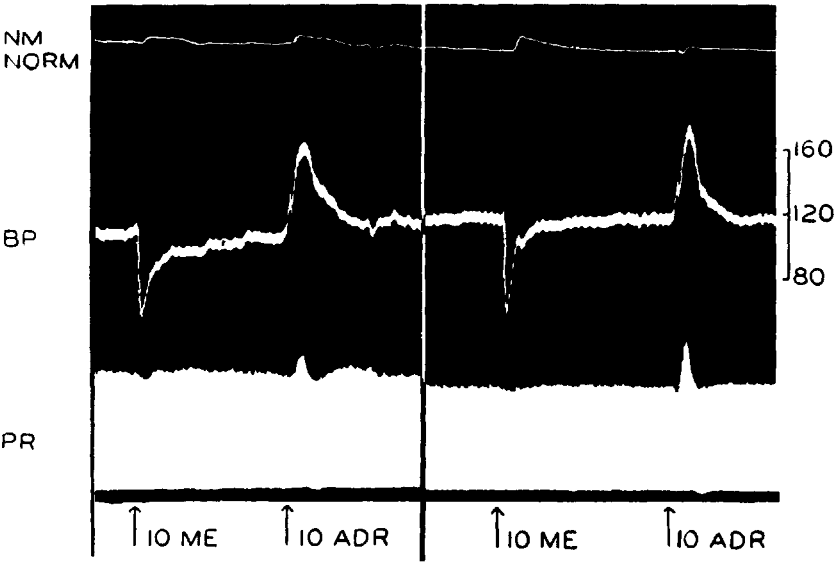

*Figure 45.* The effect of a unilateral injection of metrazol (0.04 cc., 10 per cent) into the posterior hypothalamus on the responsiveness of the blood pressure, pulse rate, and normal nictitating membrane to 10 gammas of mecholyl and 10 gammas of adrenaline i.v. (injections indicated by arrows). Note the increased sympathetic responsiveness after metrazol indicated by the more rapid recovery of the blood pressure and the greater contraction of the nictitating membrane in the mecholyl test. The peripheral action of adrenaline on the blood vessels is not changed. Metrazol was injected after the first two tests had been given, Gellhorn and Redgate (127).

becomes similar to that seen in the pre-injection control, the experiments show that the action of mecholyl, acetylcholine, and histamine on the blood pressure decreases reversibly with increasing sympathetic excitability of the hypothalamus.

## 2. The Intrahypothalamic Action of Pentothal and Procaine

A series of experiments was performed in which the action of hypotensive drugs was tested after the excitability of the posterior hypothalamus had been lowered by the injection of pentothal* and, in some instances, of procaine. Figure 46 shows the effect of acetylcholine, and Figure 47 that of histamine, on the blood pressure and the pulse rate

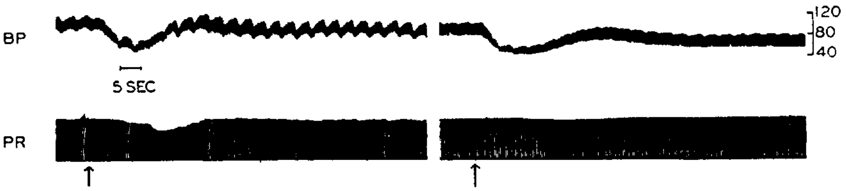

*Figure 46.* The effect of acetylcholine on blood pressure and pulse rate before and after pentothal injection into the posterior hypothalamus. Note that the hypotensive action is prolonged and the acceleration of the heart rate is absent after the excitability of the posterior hypothalamus has been reduced by pentothal. Arrows indicate injections of 5 gammas/Kg of acetylcholine i.v.

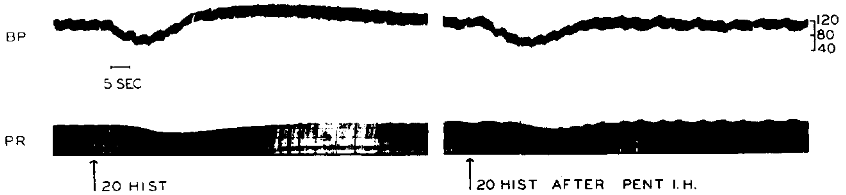

*Figure 47.* The effect of a bilateral injection of pentothal (0.04 cc., 4 per cent) into the posterior hypothalamus (between the two tests) on the responsiveness of the blood pressure and the pulse rate to 20 gammas of histamine i.v. (injections indicated by arrows). The delayed recovery of the blood pressure and the lesser acceleration of the pulse rate in the right side of the figure indicate the decreased sympathetic responsiveness after the injection, Gellhorn and Redgate (127).

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* It is assumed that the intrahypothalamically injected drugs act only on the structures into which the drugs have been injected for the following reasons: (a) The quantities used are ineffective when used intravenously. (b) The duration of their action parallels their effect on the excitability of the injected structure. (c) The effects of a drug (for instance, pentothal) injected in the anterior and posterior parts of the hypothalamus are fundamentally different as far as the vascular reactions studied in this monograph are concerned. (d) Injection of these drugs in the thalamus failed to alter these reactions.

Table 1. The Effect on the Hypotensive Action of Acetylcholine and Histamine of Injecting Drugs into the Posterior Hypothalamus

| Cat | Drug Injected into Hypothalamus | Recovery of Blood Pressure * | Pulse Rate † |  | Change in Contraction ‡ |  | Site of Injection |  |
|---|---|---|---|---|---|---|---|---|
|  |  |  | Increased | Decreased | Normal NM | Denervated NM | Distance Anterior to MB ** | Distance Dorsal to Base of Brain |
| *A. Experiments on I.V. Injection of Acetylcholine* |  |  |  |  |  |  |  |  |
| 225 | Pentothal | − | − |  | − | − | 0 mm. | 4 mm. |
| 229 | Pentothal | − | − |  | 0 | 0 | 1.5 | 2 |
| 230 | Pentothal | − | 0 |  | − | − | 1 | 2 |
| 231 | Pentothal | − | − |  | − | − | 1 | 4 |
| 236 | Pentothal | − | − |  | − | − | 0 | 1.5 |
| 244 | Pentothal | − | 0 |  | − | − | 0 | 3.5 |
| 287 | Pentothal | − | − |  | 0 | − | 0 | 2 |
| 218 | Procaine | 0 | − |  | − | − | 0 | 4 |
| 221 | Procaine | − | − |  | 0 | 0 | 0.5 | 3 |
| 215 | Strychnine | + | + |  | + | + | 0 | 4 |
| 296 | Strychnine | + | + |  | + | + | 0.5 | 3 |
| 223 | Metrazol | + | + |  | + | + | 0 | 2 |
| 240 | Metrazol | + |  |  | + | 0 | 2 | 3 |
| *B. Experiments on I.V. Injection of Histamine* |  |  |  |  |  |  |  |  |
| 229 | Pentothal | − | − |  | − | − | 1.5 mm. | 2 mm. |
| 230 | Pentothal | − | − |  | − | − | 1 | 2 |
| 231 | Pentothal | − | − |  | − | − | 1 | 4 |
| 236 | Pentothal | − |  | + | − | − | 0 | 1.5 |
| 244 | Pentothal | − | 0 |  | − | − | 0 | 3.5 |
| 288 | Pentothal | − | − |  | − | 0 | 1 | 3.5 |
| 292 | Strychnine | + | − |  | + | 0 | 0.5 | 3.5 |
| 240 | Metrazol | + | + |  | + | 0 | 2 | 3 |

* A plus sign indicates that the recovery of the blood pressure from hypotension is accelerated and/or leads to a rise above control level; a minus sign indicates the opposite.

† A plus sign indicates more acceleration or deceleration respectively; a minus sign indicates the opposite.

‡ A plus sign indicates a larger contraction; a minus sign, a smaller contraction; a zero indicates no change.

** MB = Mammillary bodies.

before and after the injection of pentothal into the posterior hypothalamus. It is seen that (a) in the acetylcholine experiment the fall of the blood pressure is more prolonged after pentothal; (b) in the histamine experiment the blood pressure fails to rise above the control level after pentothal, whereas such an "overshooting" was very marked under control conditions; and (c) the acceleration of the pulse rate in response to acetylcholine and histamine is greatly lessened after pentothal.

From the delayed return and the lesser overshooting of the blood pressure as well as from the lessened acceleration of the pulse rate, it is concluded that pentothal, when injected into the posterior hypothalamus, reduces the responsiveness of the sympathetic system to drug-induced hypotension. A survey of the experiments involving the injection of drugs into the posterior hypothalamus is given in Table 1. On the basis of the behavior of the nictitating membranes, the heart rate, and the blood pressure as sympathetic indicators, it is seen that the sympathetic discharge in response to various hypotensive drugs is fundamentally altered when drugs are injected into the posterior hypothalamus. The injection of metrazol increases this discharge, whereas the injection of depressant drugs diminishes it. Increased hypothalamic excitability is associated with a diminution of the hypotensive action* of mecholyl and related drugs, whereas the diminution of the hypothalamic excitability has the opposite effect. The drug experiments prove conclusively that the excitability of the hypothalamus has a decisive influence on the vascular action of the hypotensive drugs. In the light of these experiments, persons in Group I (in our classification of Funkenstein's mecholyl test) appear to be characterized by a hyperreactive sympathetic hypothalamus, whereas the central sympathetic excitability of Group III is subnormal; and the intermediate group constitutes the normal level of sympathetic hypothalamic excitability. Furthermore, on the basis of our experiments it is suggested that a shift from one to another of Funkenstein's groups can be accomplished by changing the excitability of the hypothalamus. These conclusions are supported by the experimental evidence presented in the following two sections.

### 3. THE EFFECT OF PHYSIOLOGICAL CHANGES IN THE EXCITABILITY OF THE HYPOTHALAMUS†

In the first group of experiments the action of mecholyl was studied in different states of hypothalamic excitability which occurred spontaneously. Periods of increased activity of lightly anesthetized animals alternated with phases of lesser activity; during the former periods, signs of awakening, such as the dilatation of the pupil and the occurrence of spontaneous movements, were associated with changes in the action potentials of the posterior hypothalamus which indicated a state of increased excitation (21). Often these phases of "awakening" were accompanied by parallel changes in the blood pressure, nictitating membrane, and the pulse rate.

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* And an early return of the blood pressure to or above the control level.

† Redgate and Gellhorn, 260.

In the experiment shown in Figure 48 the action of mecholyl on the blood pressure and the nictitating membrane was tested in a highly excitable animal in which spontaneous sympathetic discharges leading to synchronous elevations of the blood pressure and contractions of the nictitating membrane occurred (see middle section of Fig. 48). The intravenous injection of 4 gammas of mecholyl elicited a sharp fall of the blood pressure, followed by a brisk rise and an "overshooting" above the control level. The return of the blood pres-

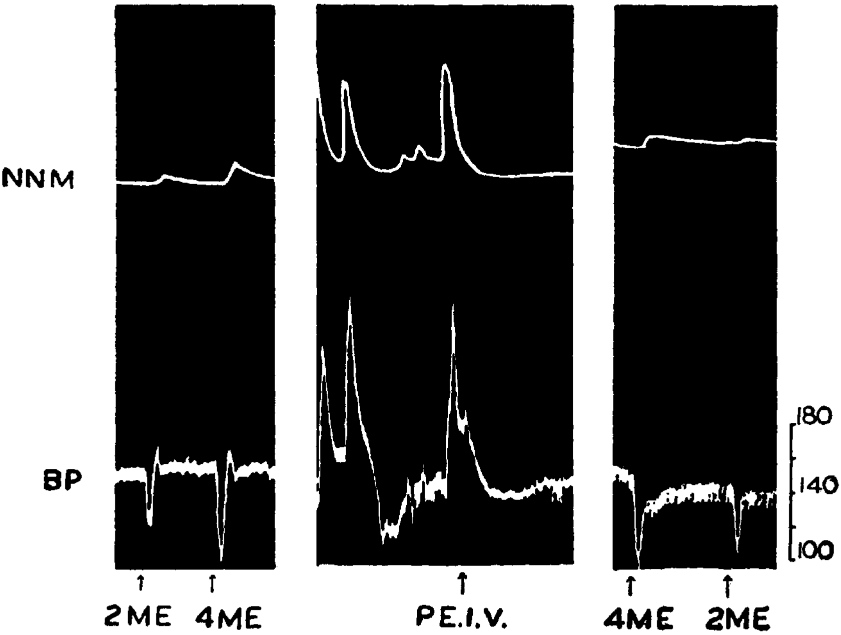

*Figure 48.* Recording of the nictitating membrane and blood pressure in response to 2 and 4 gammas of mecholyl before (left section) and after administration of 20 mg. pentothal i.v. (right section). The middle section shows spontaneous sympathetic discharges which were suppressed by pentothal. The experiment shows that the spontaneous rises of the blood pressure, and the contractions of the nictitating membrane which occur synchronously, are suppressed by pentothal and that this change is associated with a lesser sympathetic responsiveness to mecholyl, Redgate and Gellhorn (260).

sure was accompanied by a distinct contraction of the nictitating membrane. After cessation of the spontaneous hypothalamic discharges following the injection of pentothal, the hypotensive action of mecholyl was more prolonged, no overshooting took place, and the contraction of the nictitating membrane was greatly lessened.

In this experiment a phase of spontaneously increased excitability of the hypothalamus appeared to be associated with a quicker return of the blood pressure from the mecholyl-induced hypotension. A similar effect may be established by threshold or subthreshold stimulation

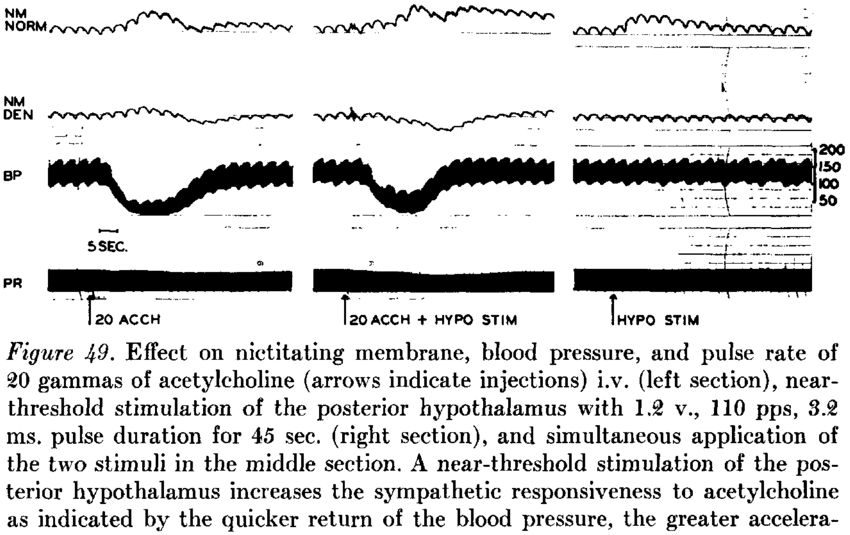

*Figure 49.* Effect on nictitating membrane, blood pressure, and pulse rate of 20 gammas of acetylcholine (arrows indicate injections) i.v. (left section), near-threshold stimulation of the posterior hypothalamus with 1.2 v., 110 pps, 3.2 ms. pulse duration for 45 sec. (right section), and simultaneous application of the two stimuli in the middle section. A near-threshold stimulation of the posterior hypothalamus increases the sympathetic responsiveness to acetylcholine as indicated by the quicker return of the blood pressure, the greater acceleration of the heart rate, and the more prolonged contraction of the nictitating membrane, Redgate and Gellhorn (260).

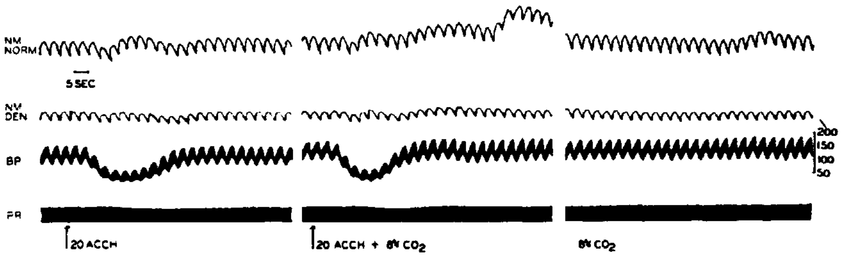

*Figure 50.* The effect on nictitating membrane, blood pressure, and pulse rate of inhalation of 8 per cent $CO_2$ (right section), injection of 6 gammas per Kg acetylcholine (arrows indicate injections) i.v. (left section) and combination of the two stimuli (middle section). Note the accelerated return of the blood pressure from the acetylcholine hypotension and the increased contraction of the nictitating membrane under the influence of $CO_2$, Redgate and Gellhorn (260).

of the posterior hypothalamus. Such an experiment is illustrated in Figure 49, the right section of which shows that the hypothalamic stimulus had no effect on the pulse rate and the blood pressure, but elicited a slight contraction of the innervated nictitating membrane. The left and middle parts of the figure show the records obtained when 20 gammas of acetylcholine was injected, with and without a simultaneous stimulation of the hypothalamus. It is evident that the duration of the hypotensive action* was greatly diminished, and that the acceleration of the pulse was greater, occurred with a shorter latent period, and lasted longer under the simultaneous influence of the near-threshold hypothalamic stimulus and the acetylcholine than in either of the control tests. Also the contraction of the nictitating membrane was more prolonged under the combined influence of acetylcholine and hypothalamic stimulation.

Finally, an experiment may be presented on the action of carbon dioxide. This experiment was performed because it was known from our earlier studies (94) that carbon dioxide in concentrations of 6 to 10 per cent increases the sympathetic hypothalamic excitability. Figure 50 shows the influence of carbon dioxide on the action of acetylcholine. For the time recorded in the figure, 8 per cent carbon dioxide had almost no influence on the pulse rate; the blood pressure remained practically unchanged, and the nictitating membrane showed a slight, late contraction. When 20 gammas of acetylcholine was injected during the inhalation of carbon dioxide, the blood pressure returned more quickly from the hypotensive phase and the contraction of the nictitating membrane was increased and prolonged. However, the acceleration of the pulse was slightly less under these conditions (see middle section). This seems to be due to the fact that under the influence of the combined stimuli the blood pressure overshot slightly and the vagal reflexes competed with the sympathetic reflexes elicited by the hypotensive action of acetylcholine.

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* Many of the experiments to be discussed subsequently illustrate the fact that the action of mecholyl and other hypotensive drugs on the blood pressure is altered under experimental conditions. The chief alterations consist in either a delay of the return of the blood pressure to the control level or an acceleration of it. The latter phenomenon is often accompanied by a brief hypertensive phase following the hypotensive phase. If experimentally the return of the blood pressure is accelerated (with or without overshooting), I speak of a lessened action of the hypotensive drugs or of a lessened hypotensive area (i.e., the area delimited by the systolic blood pressure from the beginning of the fall until its return to the control level). Conversely, if the return of the blood pressure is delayed or incomplete, I speak of the increased action of the hypotensive drugs or the increase of the hypotensive area. The variations encountered in the initial fall of the blood pressure on injection of a hypotensive drug are insignificant under our experimental conditions and may therefore be neglected. They become important only if the action of these drugs is studied at extremely different levels of the blood pressure.

The experiments described in this section seem to confirm, by means of physiological methods, the earlier experiments in which, through the injection of drugs, the excitability of the posterior hypothalamus was increased. Apparently states of increased excitability of the sympathetic division of the hypothalamus are associated with a lessened hypotensive action of drugs of the mecholyl group.

### 4. THE EFFECT OF LESIONS OF THE POSTERIOR HYPOTHALAMUS *

In 17 cats high frequency-induced lesions were placed bilaterally into the posterior hypothalamus. This procedure altered the effect of hypotensive drugs in a characteristic fashion. If the blood pressure level was the same when the pre- and post-coagulation tests with the

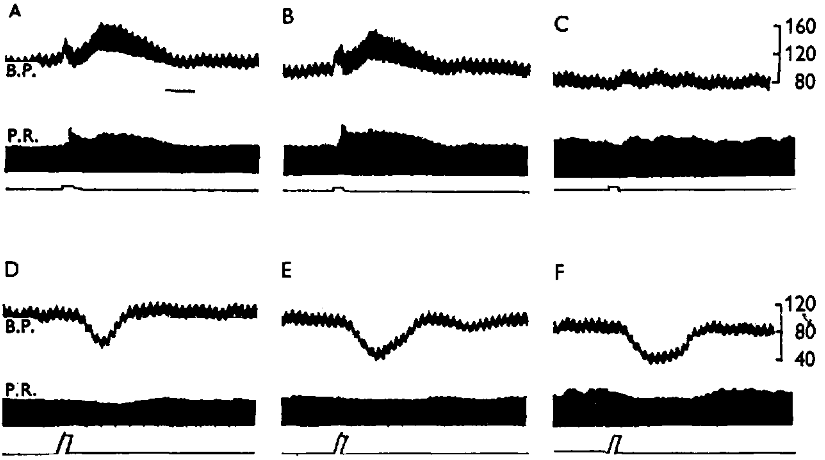

*Figure 51.* The effect of unilateral coagulation of the posterior hypothalamus (between *A* and *B*, and *D* and *E*) and bilateral coagulation of the posterior hypothalamus (between *B* and *C*, and *E* and *F*) on the excitability of the posterior hypothalamus and the action of acetylcholine. Note that with progressive coagulation the hypothalamic response to electrical stimulation progressively diminishes while the hypotensive effect of acetylcholine increases, Gellhorn, Nakao, and Redgate (125).

*A*. Left posterior hypothalamic stimulation (S.W.D., 1.0 v., 99 pps, 0.8 ms., 4 sec.) control. *B*. Same as *A* after right posterior hypothalamic coagulation. *C*. Same as *A* after left posterior hypothalamic coagulation. *D*. 5 gammas of acetylcholine control. *E*. 5 gammas of acetylcholine after right posterior hypothalamic coagulation. *F*. 5 gammas of acetylcholine after left posterior hypothalamic coagulation. Horizontal bar in *A* = 10 seconds.

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* Gellhorn, Nakao, and Redgate, 125.

hypotensive drug were performed, the hypotensive action after coagulation was increased in degree (i.e., the blood pressure fell to a lower level than in the preceding control test) and, particularly, in duration. If acetylcholine, mecholyl, or histamine elicited a contraction of the nictitating membrane under control conditions, this contraction was diminished after coagulation. The acceleration of the heart rate which accompanied the hypotensive action was likewise diminished.

Figure 51 illustrates the effect of the coagulation of the posterior hypothalamus on the action of acetylcholine and shows at the same time the relation of this effect to the excitability of the posterior hypothalamus as measured by its responsiveness to a standard stimulus. After a unilateral coagulation the pressor effect of this stimulus was slightly diminished in magnitude and duration (*B*), whereas the hypotensive area produced by acetylcholine was markedly greater in test *E* than in the control test *D*. At the same time the pulse acceleration accompanying the action of acetylcholine was reduced. After a bilateral hypothalamic coagulation the tests were repeated. The hypothalamic response to the standard stimulus was then abolished (*C*) and the hypotensive area was further increased (*F*).* These effects are like-

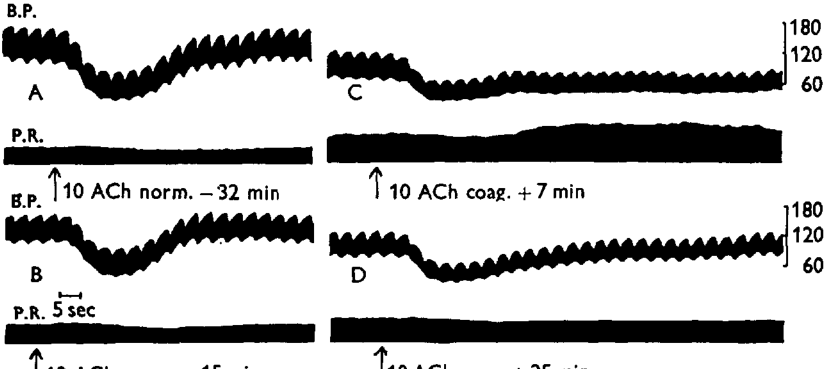

*Figure 52.* The effect of bilateral coagulation of the posterior hypothalamus on the action of acetylcholine. Note that the blood pressure is markedly lowered after the coagulation and that the hypotensive action of acetylcholine is prolonged and less reversible, Gellhorn, Nakao, and Redgate (125).

*A*. 10 gammas of acetylcholine 32 minutes before bilateral posterior hypothalamic coagulation. *B*. 10 gammas of acetylcholine 15 minutes before bilateral posterior hypothalamic coagulation. *C*. 10 gammas of acetylcholine 7 minutes after bilateral posterior hypothalamic coagulation. *D*. 10 gammas of acetylcholine 25 minutes after bilateral posterior hypothalamic coagulation.

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* Some acceleration of the pulse rate is again seen, but the level of the pulse rate has been markedly reduced.

wise seen with mecholyl and histamine as tests and are irreversible within the time limits of an acute experiment.

Frequently, as illustrated in Figure 52, the effect of a bilateral coagulation of the posterior hypothalamus was even greater. In such cases the coagulation caused a fall of the blood pressure and a slowing of the heart rate which were not reversible. Whereas in the control experiments the systolic pressure varied between 160 and 180 mm. Hg, it fell to 120 mm. Hg after coagulation. Under these conditions the relative fall of the blood pressure was less than under control conditions, but the duration of the hypotensive action was greatly increased. Figure 52 shows also that whereas acetylcholine caused an increase of the heart rate in the control tests *A* and *B*, this effect was almost completely lost in test *C* and a deceleration of the heart rate occurred during the latter part of the prolonged hypotension. In test *D*, some time later, the recovery from hypotension had improved

Table 2. The Effect of Coagulation of the Posterior Hypothalamus on the Recovery of the Blood Pressure and Pulse Rate Following the Hypotensive Action of Acetylcholine and Histamine

| Cat | Acetylcholine | | | Histamine | | |
|---|---|---|---|---|---|---|
| | Dose Gammas/Cat | Changes in | | Dose Gammas/Cat | Changes in | |
| | | Recovery of Blood Pressure* | Acceleration of Heart Rate† | | Recovery of Blood Pressure* | Acceleration of Heart Rate† |
| 284 | 10 | — | — | 10 | — | — |
| 289 | 10 | — — | + | 10 | — — | + |
| 306 | 10 | — — — | — — — | 15 | — — — | — — — |
| 340 | 5 | — — | + | | | |
| 341 | 5 | — — — | — | | | |
| 345 | 2 | — | — | 10 | — | — |
| 371 | 5 | — | 0 | | | |
| 375 | 5 | — — | — | | | |
| 379 | 5 | — — — | — — | | | |
| 381 | 10 | — — | — — | | | |
| 383 | 20 | — | 0 | | | |
| 387 | 5 | 0 | 0 | 10 | 0 | 0 |
| 390 | 10 | — | — | 5 | — — | — — |
| 391 | 5 | — | 0 | 10 | — | — |
| 394 | 5 | + | 0 | | | |
| 405 | 10 | — — | — — | 10 | — | — |
| 406 | 10 | 0 | 0 | 10 | 0 | 0 |

* The minus signs (one to three) indicate increasing degrees of delay in the return of the blood pressure to the control level, a plus sign designates a quicker return, and zero no change, as compared with the precoagulation test.

† The minus signs (one to three) indicate different degrees of lessened acceleration of the heart rate, a plus sign indicates more acceleration, and zero no change, as compared with the precoagulation test.

somewhat, the deceleration of the heart rate had disappeared, but the acceleration of the heart rate was still minimal.

Table 2 gives a survey of the action of a bilateral coagulation of the posterior hypothalamus on the acetylcholine and histamine tests. The table shows that in 14 out of 17 experiments the recovery of the blood pressure from the hypotensive action of the drugs was delayed. The greater hypotensive effect of acetylcholine was in 9 cases accompanied by a lesser acceleration of the heart rate than in the control test. The histamine (and the mecholyl tests not listed in the table) showed similar results. It should be added that the histological investigation showed that the lesions were placed in the posterior hypothalamus and involved such nuclei as the mammillaris, hypothalamicus ventrolateralis, ventromedialis, periventricularis, lateralis, and posterior.

### C. THE INFLUENCE OF THE EXCITABILITY OF THE ANTERIOR HYPOTHALAMUS ON THE ACTION OF NORADRENALINE *

The preceding experiments have led to the conclusion that the state of sympathetic hypothalamic excitability determines the degree of the hypotensive action of a given dose of a hypotensive drug. Consequently, other conditions being equal, the intensity of the hypotensive action may be used as a measure of the excitability of the posterior hypothalamus. Physiological experiments involving stimulation and elimination of the hypothalamus as well as clinical observations make it an established fact that the hypothalamus has also a profound influence on parasympathetic activity. It therefore remains to be investigated whether the excitability of the parasympathetic division of the hypothalamus can be determined in a similar manner.

The data obtained in the experiments with hypotensive drugs suggest strongly that it is the lowering of the sino-aortic pressure which calls the sympathetic division of the hypothalamus into action and thereby, as mentioned above, determines the final effect of these drugs on the circulatory system. If this interpretation is correct, one would expect a rise of the sino-aortic pressure to call forth a discharge from the parasympathetic division of the hypothalamus. On injection of a drug which raises the blood pressure (and consequently the sino-aortic pressure), the rise of the blood pressure and also the reflex slowing of the heart should be determined by the excitability of parasympathetic centers in general, and those in the hypothalamus in particular. To determine the validity of this hypothesis, alterations in the excitability of the anterior hypothalamus were induced by the

* Redgate and Gellhorn, 261.

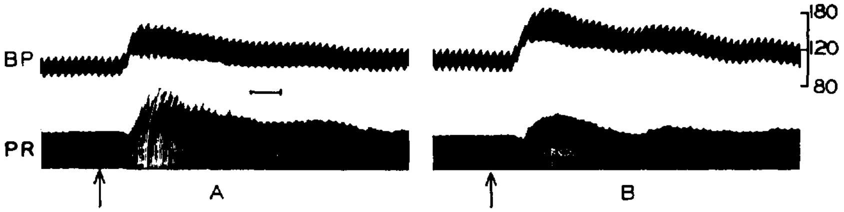

*Figure 53.* The effect of bilateral injection of pentothal into the anterior hypothalamus on noradrenaline-induced (injections indicated by arrows) reflex slowing. Note that the reflex slowing of the heart rate is lessened after the injection of pentothal in spite of the greater rise of the blood pressure, Redgate and Gellhorn (261).

*A.* 2.5 gammas of noradrenaline i.v. *B.* 2.5 gammas of noradrenaline i.v. after bilateral injection of 0.04 cc. pentothal (40 mg/cc) into the anterior hypothalamus.

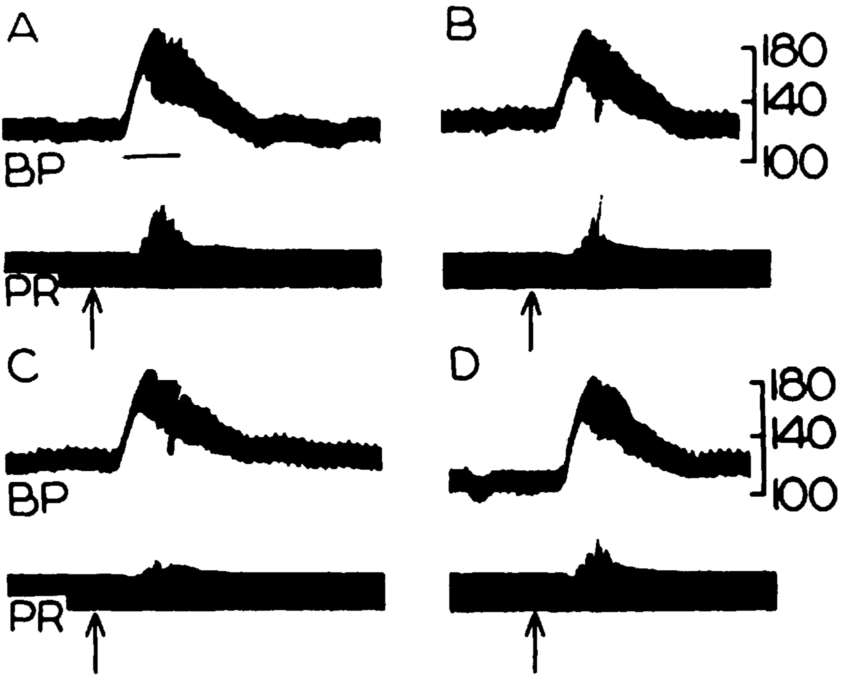

*Figure 54.* The effect of the injection of pentothal into the anterior hypothalamus on the reflex slowing caused by the noradrenaline-induced rise of blood pressure. Note that the reflex slowing progressively decreases after unilateral and bilateral injection of pentothal into the anterior hypothalamus and that this action is reversible. Pentothal is injected into the right anterior hypothalamus between *A* and *B* and into the left between *B* and *C*. Record *D* was taken 20 minutes after the last intrahypothalamic injection. At the arrow 5 gammas of noradrenaline was injected i.v., Redgate and Gellhorn (261).

injection of drugs or coagulation, and the influence of these procedures was studied on the quantitative action of noradrenaline on the blood pressure and pulse rate.

### 1. The Action of Pentothal

A typical experiment is illustrated in Figure 53. The action of 2.5 gammas of noradrenaline on the blood pressure and pulse rate is shown before and after the injection of pentothal into the anterior hypothalamus. The reduction of the excitability of the anterior hypothalamus had two decisive effects on the noradrenaline test: (a) it increased the blood pressure rise induced by this drug; (b) it diminished the reflex slowing of the pulse rate. The latter effect is the more remarkable, since it is well known that the reflex slowing of the pulse rate depends on the relative and also on the absolute rise of the sinoaortic pressure. Since in this experiment the blood pressure level was not changed by the intrahypothalamic injection of pentothal, the rel-

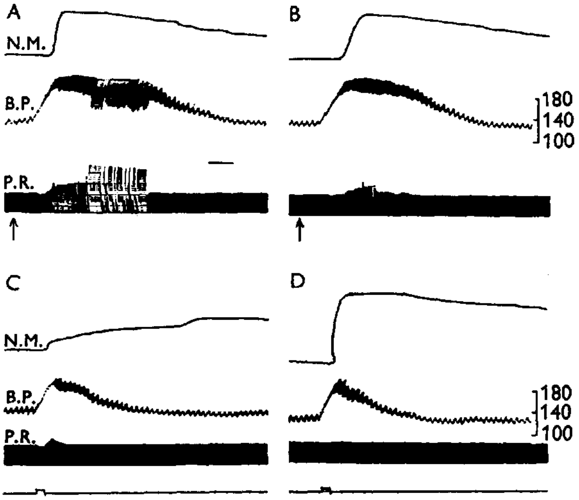

*Figure 55.* The effect of coagulation of the anterior hypothalamus between *A* and *B* and between *C* and *D* on the noradrenaline-induced reflex slowing and on the excitability of the posterior hypothalamus. Note that the reflex pulse slowing after coagulation is greatly decreased and that the excitability of the posterior hypothalamus to electrical stimulation, as indicated by the contraction of the nictitating membrane, is increased, Gellhorn, Nakao, and Redgate (125).

*A.* 10 gammas of noradrenaline at the arrow i.v. *B.* Same after bilateral anterior hypothalamic coagulation. *C.* Left posterior hypothalamic stimulation (S.W.D., 2 v., 99 pps, 0.8 ms., 4 sec.) control. *D.* Same as *C* after bilateral anterior hypothalamic coagulation.

ative *and* absolute rises of the sino-aortic pressure were greatly increased by noradenaline after pentothal. The lesser response to a stronger stimulus signifies that the reflex excitability was greatly reduced. Apparently, the excitability of the anterior hypothalamus plays a decisive role in the parasympathetic reflex slowing of the heart rate which occurs on the injection of noradrenaline.

The experiment illustrated in Figure 54 gives evidence that the action of pentothal on the anterior hypothalamus is reversible, as shown by its effect on the noradrenaline-induced parasympathetic reflex slowing of the heart rate. In addition, Figure 54 demonstrates that even a unilateral injection of pentothal into the hypothalamus diminishes the pulse-slowing reflex (*B*). When pentothal was later injected into the opposite hypothalamus, a further reduction in the vagal reflex appeared (*C*). Finally, twenty minutes after the first injection, the pulse-slowing reflex was restored to a considerable degree (*D*). These results were confirmed in numerous experiments. The sites of the injection were in the area between the optic chiasma and the anterior commissure.

*It may be concluded from these experiments that a reduction in the excitability of the anterior hypothalamus leads to a reversible diminution of the pulse-slowing reflex that occurs upon the intravenous injection of noradrenaline.*

### 2. THE EFFECT OF LESIONS IN THE ANTERIOR HYPOTHALAMUS *

Whereas sympathetic reflexes elicited through a fall of the blood pressure were diminished after coagulation of the *posterior* hypothalamus, parasympathetic reflexes were greatly reduced following the coagulation of the *anterior* hypothalamus. The noradrenaline-induced pulse-slowing reflex, which depends on the degree and duration of the rise of the blood pressure, served again as a test for parasympathetic reflexes. Figure 55 shows a typical result. Although the pressor effect of 10 gammas of noradenaline remained unaltered, the pulse slowing was greatly diminished after coagulation (*B*). The action of noradrenaline on the nictitating membrane, however, was unchanged. This fact supports the interpretation that not the peripheral action of noradenaline but the central reflex effect is altered.

It is interesting to note that the poststimulatory slowing (parasympathetic induction) seen on stimulation of the posterior hypothalamus under control conditions (*C*) failed to appear after coagulation of the anterior hypothalamus (*D*). Apparently, parasympathetic reflexes on the heart rate are diminished regardless of whether these reflexes result from a pressor effect following the injection of noradrenaline or from the stimulation of a sympathetic site of the posterior hypothalamus.

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* Gellhorn, Nakao, and Redgate, 125.

Figure 56 gives another illustration of the marked decrease in parasympathetic excitability (measured by the pulse-slowing reflex) which follows the bilateral coagulation of the anterior hypothalamus. Although the absolute rise of the blood pressure on the injection of noradrenaline was somewhat greater after coagulation than under control conditions—and this is the most effective factor in the heart-slowing reflex—this reflex was greatly reduced in tests *D* and *E* as compared with the corresponding control tests *A* and *B*.

These effects were obtained with great regularity if lesions were placed between the optic chiasma and the anterior commissure. In some instances even unilateral lesions were effective.

Summarizing the results of experiments involving either the injection of drugs into the anterior hypothalamus or the coagulation of this

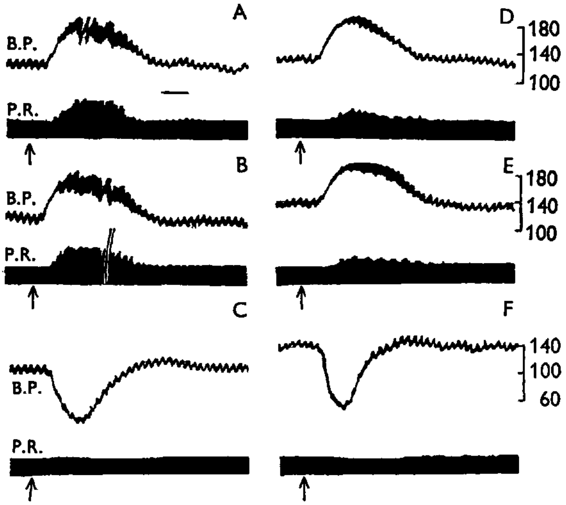

*Figure 56.* The effect of bilateral anterior hypothalamic coagulation on the reflex slowing induced by noradrenaline and on the hypotensive action of acetylcholine. Note that the noradrenaline-induced reflex slowing is diminished and that the recovery of the blood pressure from the acetylcholine-induced hypotension is accelerated, Gellhorn, Nakao, and Redgate (125).

*A.* 7.5 gammas of noradrenaline control. *B.* 10 gammas of noradrenaline control. *C.* 5 gammas of acetylcholine control. *D.* 7.5 gammas of noradrenaline after bilateral anterior hypothalamic coagulation. *E.* 10 gammas of noradrenaline after bilateral anterior hypothalamic coagulation. *F.* 5 gammas of acetylcholine after bilateral anterior hypothalamic coagulation.

structure, it may be said that procedures leading to a reduction in the excitability of the anterior hypothalamus are associated with a marked reduction in the heart-slowing reflex resulting from a rise of the blood pressure.

### D. RECIPROCAL INNERVATION AND HYPOTHALAMIC AUTONOMIC IMBALANCE

In view of the fact that a reciprocal behavior has frequently been observed between parasympathetic and sympathetic discharges in autonomic reflexes (for the literature see item 87), the question was investigated whether an autonomic imbalance created by a lesion affecting largely either the sympathetic or the parasympathetic division of the hypothalamus would influence the reactivity of the remaining intact hypothalamus. Two sets of experiments were undertaken for the study of this question. In the first, the anterior hypothalamus was coagulated and the influence of this procedure on the reactivity of the posterior hypothalamus was tested with hypotensive drugs. In the second, the posterior hypothalamus was coagulated and the function of the anterior hypothalamus was tested with noradrenaline.

Figure 57 illustrates the effect of a bilateral coagulation of the anterior hypothalamus on the reactivity to histamine. The experiment showed that the sympathetic responsiveness elicited by the hypotensive drug was greatly increased after coagulation. This is evident from the increased contraction of the nictitating membrane and the quicker return of the blood pressure, followed by a marked hypertensive phase. This latter phase is responsible for the appearance of a reflex slowing of the heart rate absent in the control test.

Figure 55 illustrates the fact that the release of the sympathetic excitability of the posterior hypothalamus which follows a coagulation in the anterior hypothalamus may also be demonstrated by testing the responsiveness of the posterior hypothalamus to electrical stimulation. A comparison between *C* and *D* of this figure shows that the contraction of the nictitating membrane was greatly increased after coagulation (*D*). The blood pressure rises were similar in the two experiments, but the parasympathetic reflex slowing which followed the period of hypothalamic stimulation in the control test (*C*) was abolished after coagulation (*D*). Since in this experiment the (already discussed) responsiveness to noradrenaline was likewise investigated, the experiment illustrates the reciprocal changes resulting from the coagulation of the anterior hypothalamus. Whereas the parasympathetic noradrenaline-induced reflex slowing was diminished, the

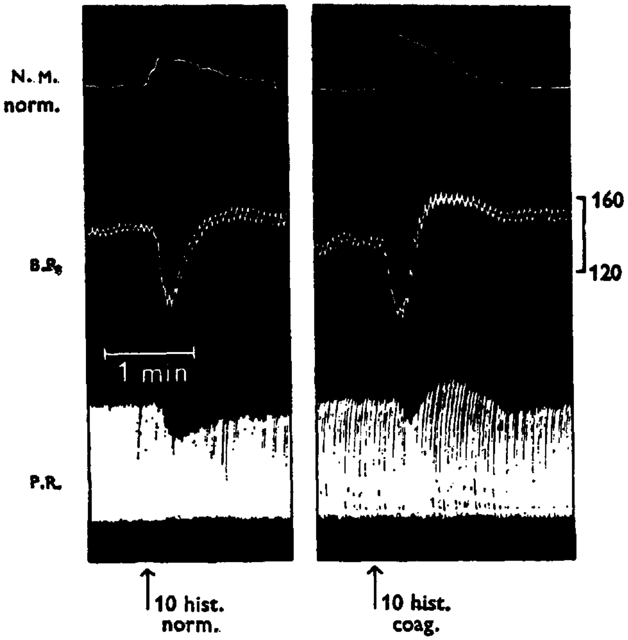

*Figure 57.* The effect of bilateral anterior hypothalamic coagulation on the action of histamine. Note that the sympathetic response to histamine indicated by the contraction of the nictitating membrane and the rise of the blood pressure following the hypotension is increased after coagulation of the anterior hypothalamus, Gellhorn, Nakao, and Redgate (125).

*Left* before, *right* after bilateral anterior hypothalamic coagulation. At the arrow 10 gammas of histamine was injected i.v.

sympathetic reactivity of the posterior hypothalamus to electrical stimulation was increased.

Figure 56, which also illustrates the marked diminution of the parasympathetic reflex on the pulse rate after anterior hypothalamic coagulation, shows at the same time (*C* and *F*) the greater reflex responsiveness of the sympathetic system to hypotensive drugs: the return of the blood pressure from the hypotensive action of acetylcholine was accelerated and the increase of the pulse rate was greater after coagulation than under control conditions.

We turn now to the group of experiments in which the *posterior* hypothalamus was coagulated and the effect of this procedure on the *anterior* hypothalamus was determined by the noradrenaline test.

It was found in numerous experiments that the noradrenaline-induced slowing of the pulse rate was intensified after bilateral coagulation of the posterior hypothalamus. The magnitude of this effect is

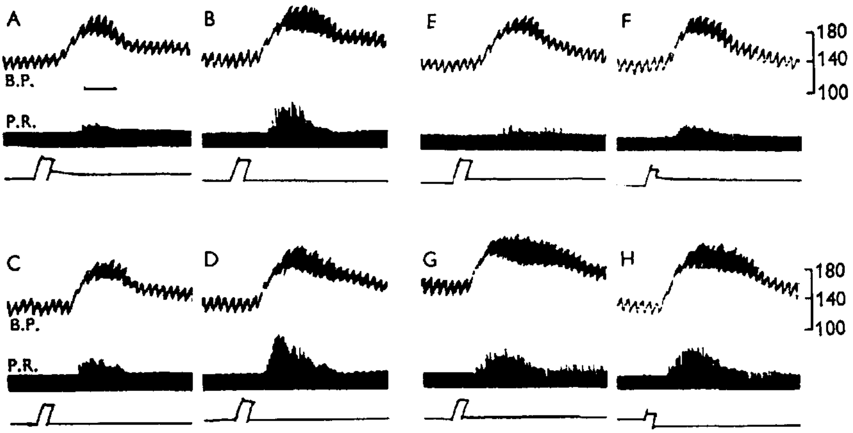

*Figure 58.* The effect of posterior hypothalamic coagulation on the reflex slowing induced by noradrenaline and the subsequent effect of nembutal injection into the anterior hypothalamus. Note that the posterior hypothalamic coagulation leads to a release of anterior hypothalamic function indicated by the greater reflex slowing in response to noradrenaline. This release of the anterior hypothalamus is abolished by injection of nembutal into this structure, Gellhorn, Nakao, and Redgate (125).

*A*. 5 gammas of noradrenaline i.v. indicated by the upward stroke of the signal magnet control. *B*. 5 gammas of noradrenaline after bilateral posterior hypothalamic coagulation. *C*. 10 gammas of noradrenaline control. *D*. 10 gammas of noradrenaline after bilateral posterior hypothalamic coagulation. *E*. 5 gammas of noradrenaline after bilateral anterior hypothalamic injection of nembutal. *F*. 5 gammas of noradrenaline 50 minutes after *E* showing recovery of reflex pulse slowing. *G*. 10 gammas of noradrenaline after bilateral anterior hypothalamic injection of nembutal. *H*. 10 gammas of noradrenaline 60 minutes after *G* showing recovery of reflex pulse slowing.

evident from the fact that in some observations the pulse rate was slowed more than under control conditions in spite of the fact that the pressor effect was lessened or the concentration of noradrenaline was decreased! Figure 58 may serve as an illustration. The control tests with 5 and 10 gammas of noradrenaline are shown in *A* and *C*, and the effects of the coagulation on these tests are shown in *B* and *D* respectively. Obviously the pulse slowing was greatly increased.* This is interpreted as due to a release of the anterior hypothalamus. If this interpretation is correct, a reduction of the excitability of this structure should diminish the pulse-slowing reflex. This was accomplished by the injection of nembutal into the anterior hypothalamus. The drug procedure was chosen in preference to the coagulation because earlier experiments had shown that the effect is similar in both cases, but that only the drug experiment is readily reversible. Tests *E* and *G* show that the depression of the anterior hypothalamic functions with nembutal abolished the increased excitability which had been produced through the coagulation of the posterior hypothalamus. The pulse-slowing reflex was restored to the control level.* Moreover, when the test was repeated after a sufficiently long interval to permit the action of nembutal to disappear, the pulse-slowing reflex was again increased (*F* and *G*), although the original effect as seen before the intrahypothalamic injection of nembutal was not attained.

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* Since in tests *B* and *D* the absolute pressure was slightly higher than in the corresponding control tests *A* and *C*, one might consider this factor and not the coagulation responsible for the greater intensity of the pulse-slowing reflex. However, a close inspection shows that this interpretation is not correct. The maximal pulse slowing in *B* and *D* occurred as the blood pressure reached the level of 180 mm. Hg, and at this pressure the pulse slowing was minimal in the control tests.

Finally attention is again called to the experiment shown in Figure 51, on the effect of hypothalamic stimulation after unilateral coagulation of the posterior hypothalamus. In addition to the expected and previously mentioned slightly lessened pressor effect (compare *B* with *A*) in response to hypothalamic stimulation it is seen that the degree of the reflex slowing of the heart rate was intensified. The dip in the pulse rate curve which in *A* accompanies the secondary large rise of the blood pressure is practically absent in *B*. Moreover, a greater degree of pulse slowing occurred in *B* than in *A* in spite of a lesser pressor effect.

From this and the previously described experiments involving the noradrenaline test, it seems to follow that after posterior hypothalamic coagulation the parasympathetic reflex excitability is increased.

## E. THE TONIC ACTION OF THE HYPOTHALAMUS ON THE BLOOD PRESSURE AND HEART RATE†

In the course of experiments involving the injection of drugs into the posterior hypothalamus, it was noted that marked changes in the blood pressure and pulse rate were temporarily produced. These experiments revealed a *tonic* function of the hypothalamus which had not been discovered previously, although the tonic action of the lower autonomic centers in the medulla oblongata is a long-established fact.

Table 3 gives a survey of our experiments on the injection of pentothal or procaine into the posterior hypothalamus. It shows that this procedure caused a considerable, reversible fall of the blood pressure.

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* The rise of the blood pressure in test *E* was slightly less than in test *B*, but the rise was greater in *G* than in *D*. Nevertheless, the pulse slowing was greatly reduced in *E* and *G* as compared to *B* and *D*. This proves that the reflex changes were due to the altered excitability of the anterior hypothalamus and not to the slight variations in the pressor responses.

† Redgate and Gellhorn, 262.

Table 3. The Effect of the Injection of Barbiturates or Procaine into the Posterior Hypothalamus on the Blood Pressure and Pulse Rate

| Cat | Drug | Systolic Blood Pressure (mm. Hg) |  | Pulse Rate/Minute |  |
|---|---|---|---|---|---|
|  |  | Control | After Injection | Control | After Injection |
| 224 | Pentothal | 170 | 130 | 145 | 80 |
| 225 | Pentothal | 124 | 100 | 127 | 165 |
| 229 | Pentothal | 140 | 60 | 163 | 135 |
| 230 | Pentothal | 120 | 70 | 140 | 120 |
| 231 | Pentothal | 160 | 100 | 127 | 163 |
| 235 | Pentothal | 130 | 70 | 135 | 127 |
| 236 | Pentothal | 155 | 100 | 100 | 125 |
| 244 | Pentothal | 135 | 95 | 163 | 100 |
| 287 | Pentothal | 120 | 60 | 120 | 110 |
| 288 | Pentothal | 120 | 60 | 163 | 130 |
| 310 | Pentothal | 140 | 130 | 215 | 200 |
| 218 | Procaine | 130 | 90 |  |  |
| 221 | Procaine | 160 | 110 |  |  |
| 350 | Pentothal | 158 | 84 | 270 | 230 |
| 359 | Nembutal | 130 | 82 | 248 | 200 |
| 363 | Pentothal | 160 | 125 | 230 | 190 |

The recovery was complete within 25 minutes in most instances. Whereas the fall of the blood pressure occurred regularly, the behavior of the pulse rate was somewhat variable. Although in most of the experiments the fall of the blood pressure was accompanied by a reduction of the heart rate, there were several cases (three out of thirteen experiments) in which the heart rate was increased. The explanation of this phenomenon seems to lie in the fact that a fall of the blood pressure will secondarily call into action the sino-aortic reflexes that will counteract the centrally induced vascular changes. It may, therefore, be assumed that the reduction or elimination of the sympathetic functions of the hypothalamus results in two opposing actions on the heart rate: (a) the loss of the accelerator tone due to the action of pentothal or procaine on the posterior hypothalamus; (b) the reflex acceleration of the pulse rate as a consequence of decreased baroreceptor reflexes resulting from the fall of the blood pressure.*

Figure 59 illustrates how markedly the blood pressure and heart rate were altered by the injection of pentothal into the posterior hypothalamus. Near the end of the record the kymograph was stopped for 25 minutes. The final recording shows that the hypotensive effect and the pulse rate slowing were almost completely reversible.

A further example of the action of an intrahypothalamically injected

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* These reflexes oppose likewise the centrally induced fall of the blood pressure.

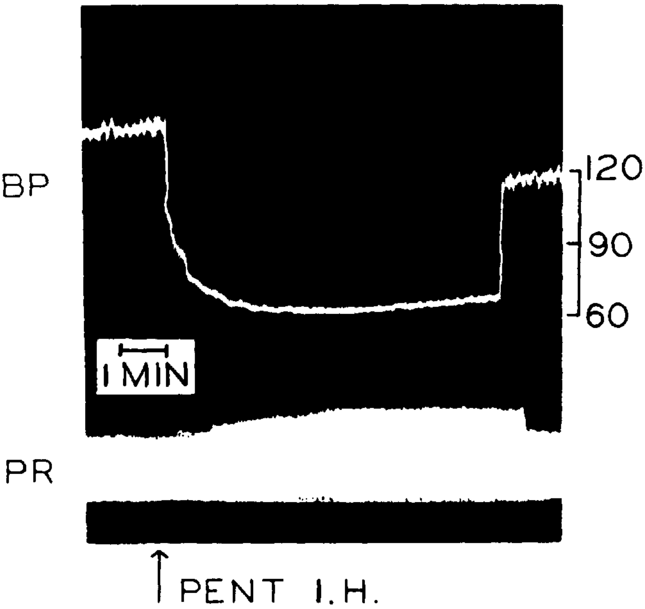

*Figure 59.* The effect of bilateral injection of pentothal in the posterior hypothalamus on blood pressure and pulse rate. 0.04 cc. 4 per cent pentothal injected at the arrow. At the end of the record, the kymograph was stopped for 25 minutes. Blood pressure and pulse rate recovered. Note that blood pressure and heart rate diminish and this effect is reversible, Redgate and Gellhorn (262).

barbiturate is illustrated in Figure 60 in which the relation between the tonic effect of the injection of nembutal into the hypothalamus is correlated with the responsiveness to acetylcholine. Section *B* shows the typical fall of the blood pressure and the corresponding slowing of the heart rate resulting from the injection of nembutal in the posterior hypothalamus, whereas *A* and *C* show the responsiveness to acetylcholine before and after the intrahypothalamic injection. In this instance dextran was injected immediately before *C* was recorded, so that it was possible to administer the acetylcholine test at the same level of the blood pressure as in test *A*, while the nembutal was still fully effective on the hypothalamus.* In spite of the influence of dextran, which has a tendency to stabilize the blood pressure, the hypotensive action of acetylcholine was greatly aggravated and the acceleration of the pulse rate seen under control conditions (*A*) was abolished.

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* In the experiments of Chapter 2, Section B, in which the effect of intrahypothalamically injected barbiturates on the action of acetylcholine, mecholyl, and histamine was studied, we waited until the tonic effect had nearly disappeared or we studied the effect in experiments in which the tonic action on the blood pressure was rather slight.

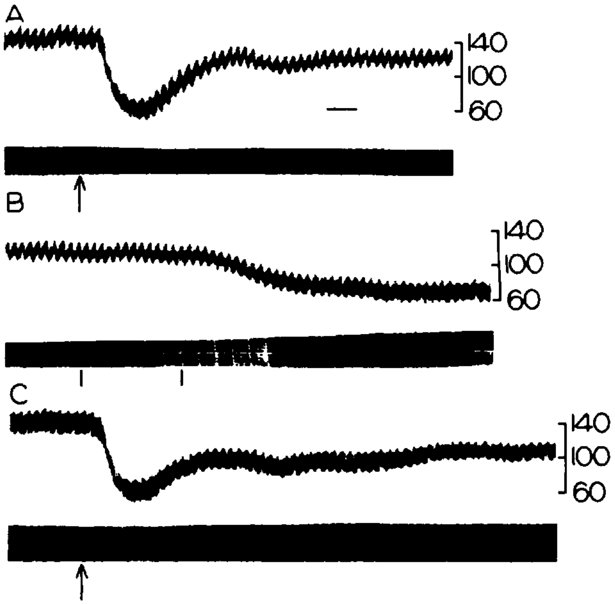

*Figure 60.* The effect of the injection of nembutal into the posterior hypothalamus on the blood pressure and heart rate. Note that the injection of nembutal into the posterior hypothalamus is followed by a fall of the blood pressure and the heart rate and by a greatly diminished sympathetic responsiveness to reflex stimulation as indicated by the failure of the blood pressure to recover from the acetylcholine-induced hypotension.

*A*. 10 gammas of acetylcholine (injection indicated by the arrow). *B*. 0.025 cc. nembutal (60 mg/cc) injected in left and right posterior hypothalamus indicated by vertical bars. *C*. 10 gammas of acetylcholine (injection indicated by the arrow) after nembutal injection and after 20 cc. dextran had been injected to provide a similar blood pressure level as in the control test *A*.

Finally an experiment should be discussed which demonstrates the effect of an intrahypothalamic injection of pentothal in an animal in which the sino-aortic receptors had at first been eliminated partially and later completely. The injection of pentothal in one side of the hypothalamus was performed after denervation of the carotid sinuses (Fig. 61*B*) whereas the injection of a similar dose of pentothal into the other side of the hypothalamus (Fig. 61*C*) was performed after bilateral vagotomy had been made in order to complete the removal of the buffer nerves. In each test the blood pressure and heart rate were lowered. Apparently even unilateral elimination of the posterior hypothalamus leads to a significant diminution of the tonic sympathetic impulses which contribute to the maintenance of the blood

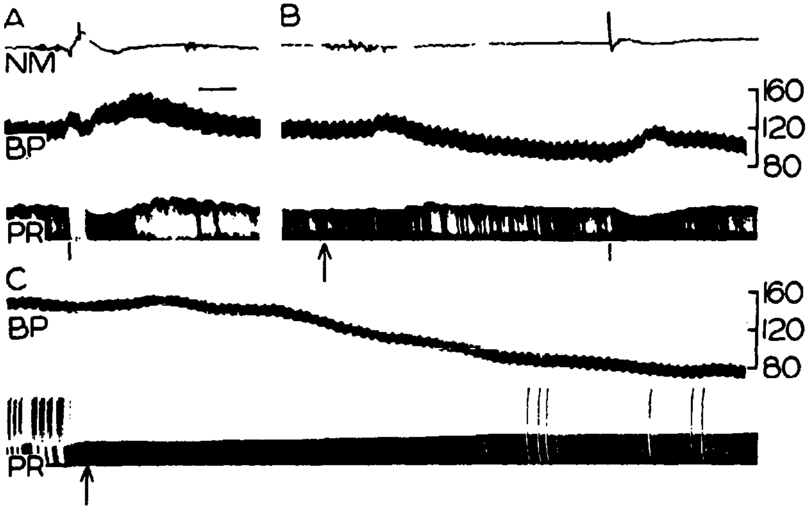

*Figure 61.* The significance of the sino-aortic buffer nerves for the tonic action of the posterior hypothalamus on the blood pressure. Note that the fall of the blood pressure in response to intrahypothalamic injection of pentothal is less marked in the partially (*B*) than in the completely sino-aortic denervated animal (*C*).

*A.* Right posterior hypothalamic stimulation indicated by a vertical line (S.W.D., 1 v., 99 pps, 0.8 ms. for 5 sec.) in a carotid sinus-denervated cat. *B.* Right posterior hypothalamic stimulation as in *A* (indicated by a vertical line) after 0.02 cc. pentothal (40 mg/cc) (injection indicated by arrow) had been injected into the right posterior hypothalamus. *C.* Between *B* and *C* the vagi were cut. At the arrow 0.02 cc. pentothal (40 mg/cc) was injected into the left posterior hypothalamus.

pressure and heart rate. It is interesting to point out that the intrahypothalamic injection of pentothal caused a slowing of the heart rate even in the vagotomized animal. This was obviously due to a diminution in the accelerator tonus of the heart.

It may be concluded from these observations that the unilateral or bilateral elimination or reduction of the excitability of the posterior hypothalamus leads to a decrease of the heart rate and blood pressure. Since the diminution of the heart rate is ordinarily greater when the vagi are intact, it is thought that the slowing of the heart rate involves a diminution of the tone of the accelerator nerve and also an increase in the tone of the vagus nerve.

Similar experiments were performed in order to determine whether the anterior hypothalamus exerts likewise a tonic function on the blood pressure and the heart rate. For this purpose pentothal or nembutal was injected into the anterior hypothalamus. The results, which are based on the maximal changes occurring within 5 to 10 minutes following the injection, show that in 7 of 12 experiments the blood pressure rose after the intrahypothalamic injection of barbiturates and that in 5 of these 7 cases the increased blood pressure was associated with an acceleration of the heart rate. In the minority of the experiments, the blood pressure and pulse rate were diminished.

In order to evaluate these data properly, it should be recalled that the functional elimination of the posterior hypothalamus by the injection of barbiturates into that structure, led, in all experiments, to a marked fall of the blood pressure. Compared with these observations the present experiments suggest that the anterior hypothalamus may exert a slight but opposite tonic function.

Finally, investigations were performed on the influence of circumscribed lesions in the anterior and posterior divisions of the hypothalamus on the blood pressure and heart rate. They confirmed and extended the observations and conclusions based on experiments involving the intrahypothalamic injection of barbiturates.

Figure 62 shows that the coagulation of the right posterior hypothalamus, undertaken in three steps as indicated in the records, produced at first the greatest effect: the blood pressure fell, while the pulse rate was decreased. By the end of the first record some recuperation had occurred. A similar effect is shown in *B*, when the coagula-

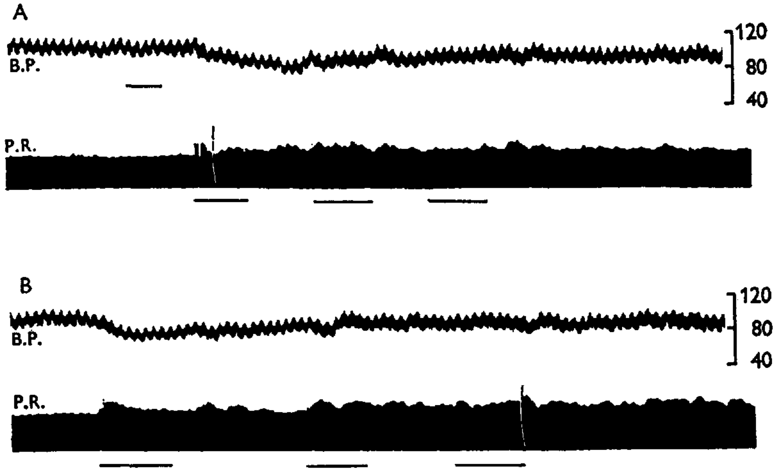

*Figure 62.* The effect of coagulation of the posterior hypothalamus on the blood pressure and pulse rate. Note that the blood pressure falls and the pulse rate becomes slower after coagulation, Gellhorn, Nakao, and Redgate (125).

*A.* Right posterior hypothalamic coagulation indicated by the horizontal line below the pulse rate (anterior, middle, posterior electrode). *B.* Left posterior hypothalamic coagulation (anterior, middle, posterior electrode).

tion of the left hypothalamus was begun. Here again some restitution is observed, but less than in *A*. By the end of *B* the blood pressure and pulse rate were distinctly below the control values.

This record is typical for all coagulation experiments, although differences occurred between individual experiments in the degree of the fall of the blood pressure and in the decrease in the pulse rate following the coagulation as well as in the degree and speed of recovery. Since the effect of coagulation at the tip of one electrode was often greater than that at the tip of another which was 1.5 mm. removed from it, one gets the impression that even within the small total lesions produced in these experiments some parts of the hypothalamus may be of greater significance for the maintenance of the tonic effects than others.

Table 4 shows the maximal effect of the coagulation, which mostly occurred within 5 or 10 minutes after the application of the high frequency currents. It indicates that after posterior hypothalamic coagulation the blood pressure fell in 16 out of 18 experiments, one unilateral and one bilateral coagulation being ineffective. However, even in these experiments there was a significant fall of the pulse rate. This rate fell in all but one experiment. It is to be noted that this method of coagulation does not involve any excitation, since, as seen in Figure

Table 4. The Effect of Posterior Hypothalamic Lesions on the Blood Pressure and Pulse Rate

| Cat | Systolic Blood Pressure (mm. Hg) | | Pulse Rate/Minute | |
|---|---|---|---|---|
| | Control | After Lesion | Control | After Lesion |
| 284 | 100 | 74 | 200 | 163 |
| 289* | 105 | 90 | 230 | 200 |
| 306 | 176 | 116 | 215 | 100 |
| 340 | 134 | 108 | 175 | 128 |
| 341 | 130 | 102 | 215 | 120 |
| 345 | 120 | 100 | 200 | 175 |
| 369* | 104 | 104 | 305 | 272 |
| 371* | 112 | 96 | 192 | 180 |
| 375 | 168 | 124 | 215 | 154 |
| 379 | 116 | 88 | 215 | 154 |
| 381* | 156 | 124 | 200 | 168 |
| 383 | 146 | 128 | 305 | 290 |
| 387 | 128 | 112 | 290 | 272 |
| 390* | 120 | 110 | 272 | 260 |
| 391 | 132 | 114 | 305 | 305 |
| 394 | 130 | 116 | 272 | 230 |
| 405 | 144 | 144 | 208 | 192 |
| 406 | 140 | 120 | 223 | 215 |

* Unilateral lesions.

Table 5. The Effect of Anterior Hypothalamic Lesions on the Blood Pressure and Pulse Rate

| Cat | Systolic Blood Pressure (mm. Hg) | | Pulse Rate/Minute | |
|---|---|---|---|---|
| | Control | After Lesion | Control | After Lesion |
| 256 | 145 | 150 | 205 | 210 |
| 257 | 90 | 130 | 180 | 240 |
| 258 | 120 | 158 | 205 | 230 |
| 386* | 108 | 124 | 185 | 175 |
| 388 | 128 | 144 | 248 | 276 |
| 393* | 100 | 112 | 285 | 305 |
| 397 | 138 | 140 | 215 | 215 |
| 398 | 120 | 128 | 185 | 200 |
| 401 | 134 | 136 | 215 | 215 |
| 402 | 116 | 144 | 200 | 230 |

* Unilateral lesions.

62 and numerous other records, the blood pressure and the pulse rate were reduced without an initial increase of either the blood pressure or the pulse rate.

Table 5 illustrates the effect of the coagulation of the anterior hypothalamus on the blood pressure and pulse rate. The effects are less marked than in the experiments listed in Table 4, but are opposite to them. Anterior hypothalamic lesions cause a temporary rise of the blood pressure and the pulse rate. This effect was absent in two experiments (cats 397 and 401) and weak in one experiment (cat 256). In the other seven experiments the rise of the blood pressure was distinct, and only in one experiment (cat 386), in which the coagulation was performed unilaterally, was the increase of the pulse rate absent. *From the experiments involving the injection of drugs and the placement of lesions into various parts of the hypothalamus, it may be concluded that the anterior and posterior divisions of the hypothalamus exert opposite tonic functions on the blood pressure and the heart rate.*

## F. INTERPRETATION

### 1. Summation Processes in Conditions of Central Autonomic Imbalance

Let us recollect first the chief pertinent experimental facts described in Chapter 2 (Section B) of this book: Lesions of the posterior sympathetic hypothalamus or injections of pentothal or procaine into this structure result in a diminished sympathetic central excitability as indicated by the lessened effectiveness of electrical stimulation of the hypothalamus and by the diminished tonic discharges leading to a (temporary) fall of the blood pressure* and a slowing of the heart rate. Under these conditions the hypotensive action of acetylcholine, mecholyl, and histamine is greatly aggravated.

On the other hand, the injection of drugs such as strychnine and metrazol into the posterior hypothalamus increases central sympathetic excitability, as tested by the response to electrical stimulation, and augments also the tonic sympathetic discharges from the hypothalamus indicated by the temporary rise of the blood pressure and the acceleration of the pulse rate. Under these conditions the hypotensive action (caused by acetylcholine and similar drugs) evokes more vigorous sympathetic reflexes (increase in the contraction of the nictitating membrane and the pulse rate), the return of the blood pressure is accelerated, and the tendency of the blood pressure to rise above the control level is increased.

In order to understand the influence of the posterior hypothalamus on the action of hypotensive drugs, the significance of tonic hypothalamic discharges for the effectiveness of hypotensive drugs must be considered more closely. These tonic discharges are revealed not only in the previously described experiments involving lesions and the injection of drugs into the posterior hypothalamus, but also in experiments in which the action of hypotensive drugs was studied over a rather wide range of blood pressure levels. In this work it was found that the recovery of the blood pressure from the hypotensive action of acetylcholine and related drugs is accelerated at high blood pressure levels. Since it may be assumed that the level of the blood pressure is directly related to the tone of sympathetic centers, it is suggested that tonic central sympathetic discharges represent an important factor which opposes the drug-induced hypotension.

The second, and obviously decisive, factor in the regulation of the hypotensive action is the sino-aortic baroreceptor reflexes. As mentioned previously, the diminution of these reflexes during a drug-induced hypotension leads to an increase of sympathetic, and to a reciprocal decrease of parasympathetic, discharges. In addition, it must be assumed that other baroreceptor reflexes play some part in the restitution of homeostasis under these conditions.†

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* The fall is temporary because of the compensatory medullary reflexes of sino-aortic origin. After the elimination of the sino-aortic receptors the fall is apparently greater and seems to be brought to a halt through other baroreceptor reflexes (158, 159, 163).

† That a direct excitation of autonomic centers in the hypothalamus, medulla oblongata, and spinal cord may be evoked in hypotension need not be stressed here, since this action of last resort to restore homeostasis is confined to more severe and prolonged degrees of hypotension than have been used in our experiments. Such severe forms of hypotension lead to the development of asphyxia.

The term "tonic discharges" from the hypothalamus and other sympathetic centers has been used for convenience in order to describe the impulses which steadily emerge from these central structures and are so strikingly reduced by coagulation or by the injection of pentothal into the posterior hypothalamus. But of course these centers in general, and the hypothalamus in particular, receive impulses constantly from cortical cerebral and cerebellar areas as well as from peripheral sense organs. Proprioceptive impulses, in particular, have been shown greatly to increase the activity of the posterior hypothalamus (21). It cannot be doubted, therefore, that these "tonic" sympathetic discharges interact with numerous phasic sympathetic discharges of varying origin, and that the latter greatly contribute to the intensity of the total central ("tonic") discharge. Now it has been shown in Chapter 1 (Section A) that sympathetic discharges summate with (and potentiate) other similar discharges and that this holds true regardless of whether they result from hypothalamic or myencephalic stimulation, reflex excitation of autonomic centers via somatic nerves, or through changes in the baroreceptor reflexes. It must be assumed therefore, that the tonic discharges of hypothalamic origin summate with the sympathetic discharges released from the inhibitory action of the baroreceptors during hypotension. These summation processes explain the fundamental fact that when the posterior hypothalamic excitability is increased, the total sympathetic action which is elicited by a drug-induced hypotension is also increased. Consequently, the hypotensive area produced by mecholyl and other hypotensive drugs is lessened, whereas a diminution of the central sympathetic discharges through the injection of pentothal into the posterior hypothalamus or through a lesion confined to this structure causes an aggravation of the drug-induced hypotensive effect (increased hypotensive area). The fact that also the pulse rate and the contraction of the nictitating membrane are increased in the former case and diminished in the latter, gives additional evidence of the correctness of this interpretation.

In the experiments described in Chapter 1 (Section B) an autonomic imbalance was created either through the stimulation of somatic nerves such as the sciatic, or, most frequently, through sino-aortic reflexes. For these conditions of imbalance the simple rule was found to be valid that in states of sympathetic dominance the excitability of the sympathetic nervous system to stimuli acting on central autonomic structures directly or reflexly is increased. As the experiments described in Chapter 2 (Section B) have shown, this rule is likewise valid for the states of sympathetic dominance produced by drug action (metrazol, strychnine) on the hypothalamus; but it also holds, and this speaks for its physiological significance, for conditions in which a state of increased sympathetic excitability of the hypothalamus was produced through near-threshold stimulation of this structure or as the result of partial awakening. In addition, the experiments on the effect of hypercapnia suggest that physiological changes in the state of the internal environment may likewise lead to a change of the balance of the autonomic centers and to corresponding changes in the quantitative action of mecholyl. Here again states of augmented central sympathetic discharges accompanying states of increased hypothalamic excitability summate with the reflex discharges and therefore account for the lessened hypotensive action of mecholyl.

It need not be pointed out in detail that the reduction of the sympathetic posterior hypothalamic discharges resulting from the injection of barbiturates or lesions in this area lessens the central sympathetic discharges and leads to a lesser total sympathetic discharge in response to a given fall of the blood pressure. Consequently, the action of the hypotensive drugs is aggravated.

The application of this kind of reasoning to the anterior hypothalamus and the noradrenaline test is obvious, but the experimental material to which this interpretation may be applied is somewhat smaller. Increased and decreased discharges of the posterior hypothalamus were attained through various procedures, but only decreased discharges induced by the injection of drugs into the anterior hypothalamus or by similarly placed coagulations were studied in an effort to produce a central (hypothalamic) imbalance involving the parasympathetic system. The reason for this limitation is that the injection of excitatory drugs frequently induced signs of increased sympathetic excitability—an understandable effect in view of the presence of parasympathetic and sympathetic neurons in the anterior hypothalamus and the neuronal connections between the anterior and posterior hypothalamus. But even this more limited material gives clear evidence that a diminished excitability of the anterior hypothalamus and consequently diminished "tonic parasympathetic" discharges summate with the phasic parasympathetic reflex which is elicited through the noradrenaline-induced rise of the blood pressure. States of centrally diminished parasympathetic excitability are, therefore, found to respond with a lesser slowing of the heart rate to a given dose of noradrenaline. On the basis of a logical extrapolation from the state of a diminished parasympathetic central excitability to that of an increased excitability, it may be said that in states of parasympathetic dominance of central origin the responsiveness to parasympathetic reflex stimuli is increased. Reflexly induced states of parasympathetic imbalance and dominance,* described earlier (Chapter 1, Section B) behaved in a similar manner.

### 2. TESTS OF HYPOTHALAMIC EXCITABILITY AND INDICATORS OF AUTONOMIC BALANCE

The experimental work discussed so far seems to justify the conclusion that tonic discharges and autonomic excitability are directly related when these functions are altered directly in the hypothalamus. Now it was shown that the action of mecholyl † on the blood pressure is determined by the summation of the central sympathetic "tonic" discharge, which is directly related to the state of excitability of the sympathetic centers and the reflexly elicited sympathetic response. Consequently if one factor, the lowering of the pressure in the sinoaortic area, is kept constant (by the injection of a standard dose of a hypotensive drug), the effect on the blood pressure and on other sympathetic indicators, such as the nictitating membrane and the pulse rate, is determined by the excitability and the degree of tonic discharges from the central autonomic structures, such as the hypothalamus. This is the reason why the study of the mecholyl action on the blood pressure gives a measure of the central (hypothalamic) sympathetic excitability in different persons. A similar reasoning applied to experiments involving the anterior hypothalamus leads to the conclusion that the noradrenaline test is a measure of central (hypothalamic) parasympathetic excitability.

If this interpretation is correct, then obviously the semi-quantitative evaluation of the autonomic functions of the hypothalamus in the intact organism is not confined to the tests employed in this study. It may seem that the specific requirement of any test for the sympathetic division of the hypothalamus would be that it elicit a sympathetic reflex.‡ However, if the central action of such a reflex were confined to the spinal cord, there would be little chance that alterations of the rate of the sympathetic discharge from the hypothalamus would affect the reflex discharge significantly. The tests employed in this study which appear to be satisfactory indicators of the state of autonomic hypothalamic excitability involve the hypothalamus and even the cortex.* These structures are also involved in the galvanic reflex (51) and in the action of nociceptive stimuli (101, 201), and both reflexes have been shown to be altered in different emotional states (179, 287).

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* As discussed on p. 101, we succeeded in producing a state of increased parasympathetic discharges from the anterior hypothalamus by lesions of the posterior hypothalamus. As predicted, it was found under these conditions that the intensity of the noradrenaline-induced pulse-slowing reflex was augmented.

† For the sake of simplicity we speak of mecholyl instead of mecholyl, acetylcholine, or histamine.

‡ The following comments are also valid for the parasympathetic division of the autonomic system, if applied correspondingly.

### 3. RECIPROCAL INNERVATION IN STATES OF CENTRALLY INDUCED AUTONOMIC IMBALANCE

Regarding the principle of reciprocal innervation in central autonomic processes, the following experimental data should be remembered. Anterior hypothalamic lesions are associated not only with a diminished parasympathetic reflex responsiveness (tested with the noradrenaline heart-slowing reflex) but also with an increased responsiveness to sympathetic reflexes (tested with hypotensive drugs). Moreover, the direct stimulation of the posterior hypothalamus elicits increased sympathetic discharges after an anterior lesion. These observations show that the sympathetic functions of the posterior hypothalamus are released under conditions in which the parasympathetic functions of the anterior hypothalamus are diminished. This release appears not only in the phasic responses but also in the tonic sympathetic discharges of the posterior hypothalamus: Lesions in the anterior hypothalamus cause increased blood pressure and pulse rate.

Similar data were presented in evidence of the release of parasympathetic functions following bilateral lesions of the posterior hypothalamus. The reflex slowing of the heart rate is intensified under these conditions regardless of whether the reflex is due to a rise of the sinoaortic pressure resulting from the injection of noradrenaline or from stimulation of the posterior hypothalamus. The release of parasympathetic functions influences also the resting level of the blood pressure and heart rate. The pulse slowing and the fall of the blood pressure which occur after lesions in the posterior hypothalamus are not solely due to a diminution of the tonic sympathetic impulses on the heart and the blood vessels but also to increased parasympathetic impulses. This explains the fact that the elimination of posterior hypothalamic sympathetic functions through the injection of pentothal or through high-frequency lesions causes a lesser fall of the blood pressure and the pulse rate after vagotomy than when the vagi remain intact.

The increase of parasympathetic reactivity after sympathetic hypothalamic lesions and the increase of sympathetic reactivity after parasympathetic hypothalamic lesions show the validity of the principle of reciprocal innervation for the regulation of autonomic processes at the hypothalamic level.

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* See Chapter 7, Section E.

The previously described experiments on reflex tuning of the autonomic system furnished numerous demonstrations of the validity of the principle of reciprocal innervation for conditions of reflexly induced states of autonomic imbalance. Similar reciprocal relations were discovered when the tuning of the autonomic nervous system was achieved through changes in the internal environment, such as in asphyxia. The increased responsiveness of the sympathetic system in this condition to direct stimuli (hypothalamic) or reflex stimuli (acetylcholine-induced hypotension) was accompanied by a lessened response to parasympathetic stimuli. This statement applies equally to parasympathetic reflexes on the heart rate, the hypotensive action elicited by stimulation of the central end of the sciatic nerve with low frequencies, and the earlier-described phenomenon of parasympathetic induction.

It may, therefore, be said that reflexly and centrally induced states of autonomic imbalance reveal the fact that the law of reciprocal innervation regulates the relative intensity of parasympathetic and sympathetic discharges. In addition, these investigations have shown that the more the sympathetic reactivity deviates from the norm, the more the parasympathetic reactivity deviates,* and vice versa. It should be emphasized that this presentation of the state of autonomic imbalance is derived from acute experiments. Whether the investigation of chronic states of autonomic imbalance may lead to quantitatively different results remains to be seen.

## 4. The Tonic Functions of the Hypothalamus

Whereas the tonic function of the vagal nucleus and the sympathetic centers of the medulla oblongata has long been established (see item 164 for the literature), the like function of the hypothalamus on both divisions of the autonomic nervous system has not been assumed. In fact, most investigators report that the sectioning of the brain stem above the medulla oblongata is without influence on the blood pressure. Several reasons seem to account for the absence of clear effects from sectioning procedures. First, if the anesthesia is deep, hypothalamic functions are so depressed that their surgical elimination remains ineffective. Second, the transection of the brain stem with the knife involves stimulation, and this effect may counteract the fall of the blood pressure which would have been observed if a nonirritating procedure, such as the high-frequency current, had been applied. When lesions were produced by means of a high-frequency current in the anterior or posterior hypothalamus, or when through the injection of drugs into these structures their excitability was temporarily reduced or abolished, the recording of the blood pressure and heart rate showed changes which indicated that both divisions of the hypothalamus exert a tonic function. It was found that the tonic function of the posterior hypothalamus is greater than that of the anterior hypothalamus. The loss or reduction of sympathetic tonic impulses from the posterior hypothalamus appeared as a fall of the blood pressure* and heart rate, whereas a reduction of the parasympathetic functions of the anterior hypothalamus caused a rise of the blood pressure and an increase of the heart rate. Such effects may also occur after unilateral hypothalamic lesions.

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* It is likely that the increased parasympathetic discharges are not confined to the action on the heart rate which served as an indicator of such discharges in our experiments but appear also in the form of a vasodilation. Perfusion experiments of the type which has been used so successfully by Folkow and Uvnäs (71) should contribute to a further insight into the autonomic changes in conditions of autonomic imbalance of various origins.

It should be stressed that the parallel changes of the blood pressure and pulse rate are characteristic for centrally induced changes of the autonomic system. In contradistinction, reflexly induced changes of the vascular system commonly show opposite changes of the blood pressure and heart rate. Thus bleeding will lead to a fall of the blood pressure, associated with an acceleration of the pulse rate. Conversely, if the blood pressure is raised by an increase of the circulating volume (dextran, serum), the blood pressure rises while the pulse rate falls.

Although a detailed analysis of the role of sympathetic and parasympathetic impulses in the maintenance of tonic hypothalamic functions has not been made, a comparison between normal and vagotomized animals with respect to the behavior of the blood pressure and the heart rate following the injection of drugs or lesions in specific parts of the hypothalamus suggests that the effect of posterior lesions is in part due to a decrease of sympathetic impulses affecting the heart and blood vessels but in part also due to increased vagal discharges. Correspondingly, a diminution in parasympathetic discharges and an increase in sympathetic impulses seem to account for the increase of the blood pressure and the heart rate following a diminution of the tonic activity of the anterior hypothalamus.

It is generally admitted that excitatory processes of emotional origin which appear to be related to sympathetic diencephalic discharges occur frequently in the history of the patient with hypertension. Nevertheless, the majority of students of this problem see little relation between such diencephalic events and the final disease. Although a thorough discussion of the subject is beyond the task of this monograph, some remarks may not be out of place.

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* See item 312 for similar clinical effects of hypothalamic lesions.

Many authors will probably agree with Nickerson (248) that "emotionally initiated sympatho-adrenal activity" plays an important role in hypertension.* Since tonic sympathetic discharges originate in the hypothalamus, it may be said that emotional excitement leads probably not only to momentary phasic but also to increased tonic sympathetic discharges. These may well cause the renal changes which are characteristic of human hypertension.

It seems desirable to approach the problem of hypertension experimentally in a different manner. Instead of producing a "neurogenic" hypertension through release of the sympathetic central structures, as in the experiments of Koch and Mies (198), the structures themselves ought to be subjected to chronic stimulation. Thus far only Taylor and Page (292) have used the latter procedure, by stimulating the medulla oblongata. In view of the fact that the hypothalamus and not the medulla oblongata is directly involved in emotional excitement an attempt to produce a neurogenic hypertension through chronic stimulation of the posterior hypothalamus seems logical. This important experiment has not yet been performed.

The failure of Walker *et al.* (305) to alter significantly a neurogenic hypertension through hypothalamic lesions should not be taken too seriously, since extensive lesions affecting the posterior hypothalamus bilaterally were not accomplished. This type of lesion is that through which, in our work, the existence of tonic sympathetic discharges has been proved. Such lesions may be expected to lower the blood pressure in states of neurogenic hypertension.

The suggestion that chronic stimulation of the posterior hypothalamus may initiate the processes underlying the clinical syndrome of hypertension is supported by recent work. Schunk (273) exposed cats to barking dogs daily for several months, a procedure that leads to a strong excitation of the posterior hypothalamus (9). In a considerable number of the cats, the blood pressure was above normal and the heart enlarged. Moreover, histological changes in the anterior hypophysis suggest that alterations in the secretory functions of the anterior hypothalamus, possibly initiated by the overreactivity of the hypothalamus, were likewise induced.

In this connection should be mentioned an observation of Wilkins

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* Taylor *et al.* (292) state that "neurogenic hypertension has been defined as a common and early phase of essential hypertension." The findings of Smithwick and Casteman (286) that renal vascular changes follow but do not precede hypertension give added weight to these central sympathetic factors.

(318), who noticed that the adrenaline- or noradrenaline-induced slowing of the heart rate is lessened in hypertension. One might think of explaining these results on the basis of a central autonomic imbalance, since this reflex has been shown in our work to depend on the excitability of the anterior hypothalamus. Moreover, it has been emphasized that in an experimentally induced imbalance of the autonomic nervous system at the hypothalamic level, the excitability of the anterior hypothalamus was found to be reciprocally related to that of the posterior hypothalamus. In cases of increased sympathetic discharges of the posterior hypothalamus one would, therefore, expect a diminished reactivity of the anterior hypothalamus and, consequently, a lessening of the noradrenaline-induced slowing of the heart rate. However, Wilkins reported also that the noradrenaline-induced slowing of the heart rate was restored in hypertensive patients after sympathectomy. Since the elimination of the peripheral sympathetic outflow does not alter the intensity of the central discharges and thereby, through reciprocal action, the reflex sensitivity of the parasympathetic division of the hypothalamus, the explanation of Wilkins' findings must be sought in peripheral conditions: the vagal reflex is relatively ineffective in hypertensives on account of the massive sympathetic discharges which bombard the heart. The elimination of these discharges through sympathectomy makes it possible for the vagal reflexes to slow the pulse rate. Since this slowing is similar to that seen in normal persons, there is at present no evidence that in hypertension the excitability of the anterior hypothalamus is altered.

## CHAPTER 3

# THE RELATION OF HYPOTHALAMIC EXCITATION TO NEUROGENIC AND HORMONAL (ADRENOMEDULLARY) DISCHARGES. A Contribution to the Study of Homeostasis

IT IS generally accepted that appropriate excitation of the centers of the autonomic system leads to a sympathetico-adrenal discharge. This discharge occurs in emotional excitement and in conditions in which the internal environment has been changed (for instance in cold, anoxia, and hypoglycemia), and it contributes to the restitution of the physiological state of the organism. The sympathetic discharges are easily recognized by the increase of the blood pressure and heart rate, the inhibition of the gastrointestinal tract, the contraction of the nictitating membrane, the dilatation of the pupils, and piloerection, to mention only a few symptoms. The secretion of the adrenal medulla is apparent from the alteration of the function of acutely or chronically denervated organs such as the pupil and nictitating membrane (142), the heart (41), and the spleen (259), and through anastomosis experiments (227) in which the blood of the adrenal vein of one dog (I) is connected with the jugular vein of another dog (II). Excitation of the centers of the sympathetic system in dog I will lead to changes in the vascular and other functions of dog II which are based on the quality and quantity of the secretion of the adrenal medulla.

For the problems discussed in this monograph and for the more precise understanding of the autonomic nervous system in physiological and pathological conditions, it is necessary to analyze separately the role of the neurogenic and adrenomedullary discharges. This analysis and its significance for the understanding of the mecholyl test under various experimental and clinical conditions will be attempted in the present chapter.

NOTE: The basis of this chapter is unpublished work in collaboration with E. S. Redgate.

## A. THE RELATION BETWEEN SYMPATHETIC AND SYMPATHETICO-ADRENAL DISCHARGES

In contradistinction to Cannon's teaching, it was shown in an earlier study (107) that the sympathetic system may discharge not only as a whole but in the parts of the body to which the excitation may be specifically confined. Stimulation of different areas of the central nervous system—hypothalamus, medulla oblongata, and spinal cord—may, for instance, elicit a contraction of the nictitating membrane without evoking a dilatation of the pupil at the same time. It was further shown that such ocular symptoms may be dissociated from a sympathetic action on the blood pressure, and the latter may be observed without evidence of sympathetic action on ocular structures. These observations on partial sympathetic discharges suggest that the hormonal and neurogenic components * may be altered independently. Before these matters are discussed, it seems advisable to show that increased excitation of the sympathetic centers will bring about a transition from sympathetic discharges to sympathetico-adrenal discharges.

In most experiments the effect of increasing stimulation of the posterior hypothalamus was studied. As the voltage was increased, the height and duration of the contraction of the nictitating membrane increased. The rise of the blood pressure was very small in parts *A*, *B*, and *C* of the experiment, but considerable in *D* (Fig. 63). The pulse rate was practically unaltered in *A* and *B*, slightly increased in *C*, and distinctly augmented in *D*. Finally, and most importantly for the present discussion, the denervated nictitating membrane—the indicator of adrenomedullary secretion—was unchanged in *A*; a questionable or minimal contraction occurred in *B* and *C*, and a marked contraction in *D*.† Increasing intensities of stimulation led to effects ranging from a partial sympathetic (neurogenic) action to a generalized sympathetico-adrenal discharge.

These results have been confirmed in numerous similar experiments. The variable employed need not be the voltage in order to obtain the conversion from a neurogenic to a sympathetico-adrenal discharge. Other parameters may be altered instead.

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* It has been discussed elsewhere (94) that the neurogenic discharges are mediated by noradrenaline liberated at the sympathetic nerve endings, and the adrenomedullary discharges by the secretion of noradrenaline and adrenaline in various quantities. However, the separation into neurogenic and hormonal factors seems to be justified, since the former exerts only a local action (except under conditions of excessive stimulation) but the latter a generalized action in the organism.

† In the experiments shown at *C* and *D* of Figure 63 and in numerous other experiments (see Fig. 66*A* to *C*, and Fig. 67*C*), it was noted that the contraction of the denervated nictitating membrane, occurring after a long latent period, was preceded during the stimulation period by a sudden relaxation. Some observations by Dr. Redgate suggest that the relaxation is due to the liberation of acetylcholine.

If it is correct that increased excitation of the sympathetic centers leads gradually from sympathetic to sympathetico-adrenal discharges, such a transition should be obtained in various forms of sympathetic excitation and summation. The following observations are in agreement with this assumption. Varying the duration of the stimulus (asphyxia), it was found that asphyxia of increasing duration will first lead to a sympathetic and then to a sympathetico-adrenal discharge. These discharges may occur during asphyxia or immediately upon the readmission of air.

The summation of hypothalamic sympathetic stimulation and asphyxia may induce a sympathetico-adrenal discharge.

As shown in Figure 64, asphyxia of 60 seconds (*C*) caused a rise of the blood pressure and, in the second half of the experiment, a gradual contraction of the normal nictitating membrane, indicating a sympathetic discharge. The hypothalamic stimulus, when given by itself, likewise caused such a discharge, as indicated by the abrupt but submaximal contraction of the normal nictitating membrane (*B*). When the two stimuli were combined, the hypothalamic stimulus being applied during asphyxia (*A*, *D*), the summation resulted in a greater contraction of the normal nictitating membrane but also in a distinct

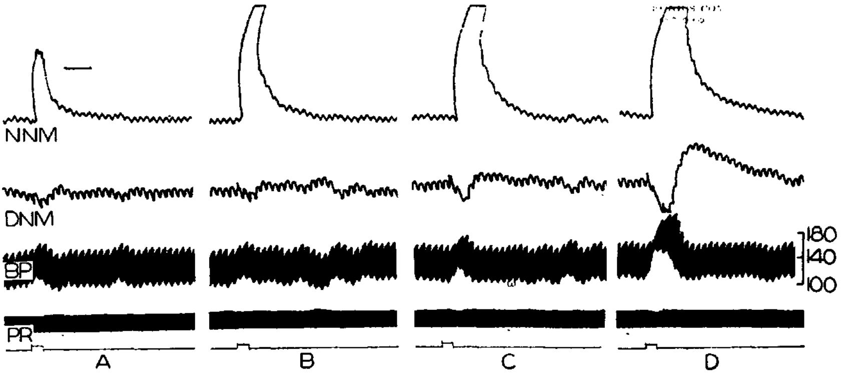

*Figure 63.* The effect of increasing voltage of hypothalamic stimulation on the sympathetic activity. Note that with increasing excitation a partial sympathetic effect is converted into a generalized sympathetico-adrenal discharge (the latter being indicated by the contraction of the denervated nictitating membrane.

*A*. Right posterior hypothalamic stimulation (0.3 v., 158 pps, 0.2 ms., 5.0 sec.). *B*. Right posterior hypothalamic stimulation (0.5 v., 158 pps, 0.2 ms., 5.0 sec.). *C*. Right posterior hypothalamic stimulation (0.7 v., 158 pps, 0.2 ms., 5.0 sec.). *D*. Right posterior hypothalamic stimulation (1.3 v., 158 pps, 0.2 ms., 5.0 sec.).

contraction of the denervated nictitating membrane, the latter occurring after the neurogenic discharge had been completed. A sympathetico-adrenal discharge resulted when both stimuli were combined, although each by itself elicited only a neurogenic discharge.

Previous parts of this monograph have emphasized that hypotensive drugs elicit a sympathetic discharge dependent upon the excitability of the autonomic centers. If we apply this information to the thesis under discussion, that increasing excitation of the sympathetic system leads from a sympathetic to a sympathetico-adrenal discharge, we should expect to find that the reflex excitation of the sympathetic system through hypotensive drugs induced a sympathetico-adrenal discharge if performed under conditions of asphyxia. That it does so is shown by the experiment illustrated in Figure 65. Acetylcholine by

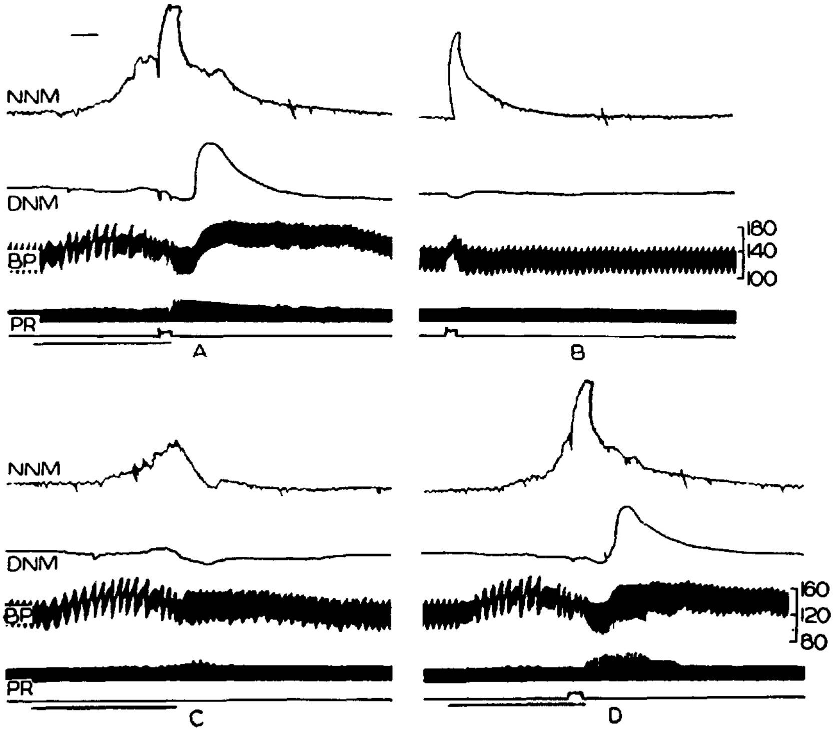

*Figure 64.* The effect of hypothalamic stimulation during asphyxia. Note that a hypothalamic stimulus, which elicits a partial sympathetic discharge under control conditions (*B*), evokes a sympathetico-adrenal discharge in asphyxia (*A, D*).

A. 60 seconds asphyxia (horizontal line) with left posterior hypothalamic stimulation (2 v., 207 pps, 0.8 ms., 5 sec.). *B*. Left posterior hypothalamic stimulation (2 v., 207 pps, 0.8 ms., 5 sec.). *C*. 60 seconds asphyxia. *D*. Same as *A*.

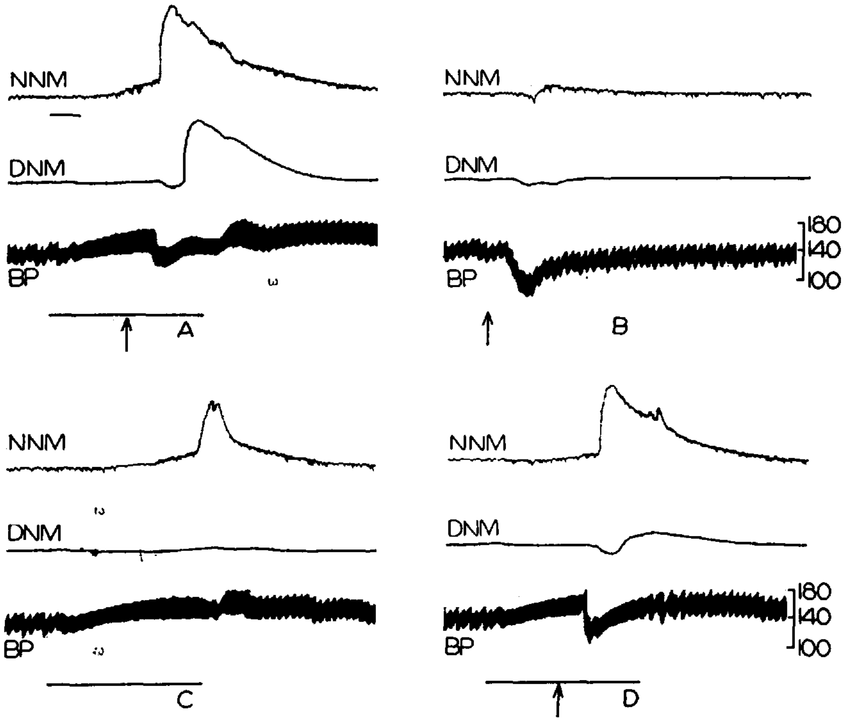

*Figure 65.* The effect of acetylcholine during asphyxia. Whereas acetylcholine does not activate the nictitating membranes in the control test (*B*), it intensifies the sympathetic discharge and leads to the appearance of adrenomedullary secretion indicated by the contraction of the denervated membrane when administered in asphyxia (*A*, *D*).

*A*. 60 seconds asphyxia (horizontal line) with 10 gammas of acetylcholine (arrow) 30 seconds after the beginning of asphyxia. *B*. 10 gammas of acetylcholine. *C*. 60 seconds asphyxia. *D*. 60 seconds asphyxia with 10 gammas of acetylchloline as in *A*.

itself did not lead to any changes in the state of the nictitating membranes (*B*), and asphyxia by itself (*C*) caused only a moderate sympathetic effect as indicated by the contraction of the normal nictitating membrane occurring when air was readmitted. But the combination of the two had very striking effect on both membranes: it greatly increased the contraction of the normal nictitating membrane and also decreased its latent period; furthermore, it caused the appearance of a contraction of the denervated nictitating membrane (*A*, *D*). Apparently, reflex stimulation of the sympathetic system through a hypotensive drug as well as direct stimulation of the sympathetic centers may cause a sympathetico-adrenal discharge in asphyxia, although each of the stimuli employed by itself causes only a sympathetic response.

Another series of experiments confirms the conclusions arrived at in the preceding work. Stimulation of the posterior hypothalamus was combined with reflex excitation of the sympathetic system through a hypotensive drug. Under these conditions it was found that the combined, but not the individual, stimuli caused a sympathetico-adrenal discharge.

In summary, reflex stimulation (through hypotensive drugs) and direct excitation of the hypothalamic sympathetic centers summate in a variety of conditions. This summation is manifested in the form of greater sympathetic excitation and also in the appearance of a humoral secretion from the adrenal medulla that was absent when the direct or reflex stimulus was applied by itself.

In the experiments described earlier* it was shown that various procedures of "tuning" may alter the responsiveness of the sympathetico-adrenal system. If it is correct that a sympathetic discharge follows mild excitation, and a sympathetico-adrenal discharge strong excitation, of autonomic central structures, changes in the excitability of these structures (the stimulus remaining the same) should effect alterations in the type of autonomic discharge. Thus, if the sympathetic hypothalamic excitability is raised, a change from the sympathetic to sympathetico-adrenal discharge should occur, whereas the reverse change should result when the excitability of hypothalamic sympathetic centers is reduced. To test this hypothesis the influence of "sympathetic tuning" through the intrahypothalamic injection of metrazol and, in a subsequent test, the action of "parasympathetic tuning" through the injection of dextran were employed in the experiment shown in Figure 66.

The hypothalamic test stimulus (*A*) elicited a sympathetico-adrenal response, as shown by the nictitating membranes, but the hormonal response (see the denervated nictitating membrane) was very small. After the sympathetic excitability of the posterior hypothalamus had been raised through the injection of metrazol, the sympathetic responsiveness of the membranes and of the blood pressure was greatly increased and a large increase of the hormonal response occurred (*B*). This effect was reversible, and some time later (*C*), after the metrazol effect had worn off, a sympathetic response similar to that seen in the control test (*A*) was observed. Thereafter dextran was injected intravenously in order to induce a parasympathetic tuning via the sino-aortic reflexes. Under these conditions the sympathetico-adrenal response was converted into a sympathetic response (contraction of the normal

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* See page 15ff and 81ff.

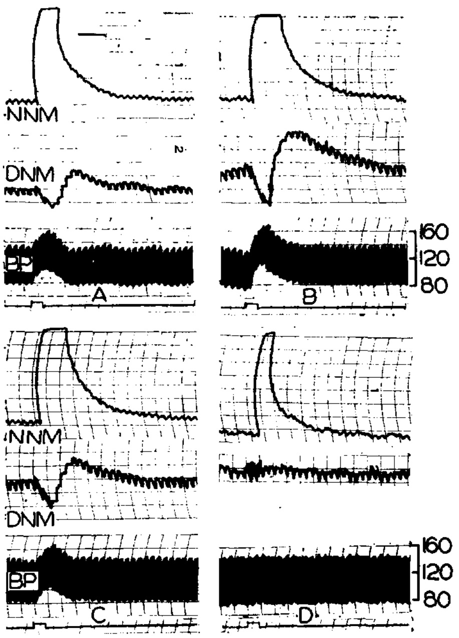

*Figure 66.* The effect of the injection of metrazol into the posterior hypothalamus on the effect of a hypothalamic stimulus. Note that the sympathetico-adrenal response to hypothalamic stimulation, after metrazol, is increased. Also, test *D* shows that after dextran the sympathetico-adrenal discharge is reduced to a sympathetic discharge.

*A*. Right posterior hypothalamic stimulation (1 v., 207 pps, 1.6 ms., 5 sec.). *B*. Same as A after 10 per cent metrazol (0.025 cc.) had been injected in left and right posterior hypothalamus. *C*. Same as *A* after recovery. *D*. Hypothalamic stimulation as in *A* after 20 cc. of dextran had been injected.

but not of the denervated nictitating membrane). It is notable that this striking effect occurred even though the administration of dextran did not increase the systolic blood pressure but only the pulse pressure.

Similar changes in the response of the sympathetic system were obtained with tuning through noradrenaline. The diminished reactivity of the sympathetic centers under these conditions changed the pattern of response in the expected direction. If the stimulus chosen produced a sympathetico-adrenal response under control conditions, its effect was reduced to a sympathetic response during the noradrenaline tuning.

It has been assumed in this discussion that the appearance of a contraction of the denervated nictitating membrane is due to an adrenomedullary secretion, since the sensitivity of this denervated structure has frequently been used as a test of the presence of circulating neurohumors (42, 259). To ascertain the correctness of this intrepretation under the special conditions of our work, experiments were performed on the influence of adrenal ligation on the action of those stimuli which in the cat with intact adrenal circulation led to a contraction of the denervated nictitating membrane. It was found that the contraction of the denervated membrane following hypothalamic stimulation was abolished through the ligation of the adrenal veins, although the normal nictitating membrane remained responsive. Similar results were obtained in asphyxia. The contraction of the denervated nictitating membrane, therefore, is due to the adrenomedullary secretion which was evoked in this work either by hypothalamic stimulation or asphyxia.

## B. THE INFLUENCE OF CENTRAL SYMPATHETIC AND SYMPATHETICO-ADRENAL DISCHARGES ON THE ACTION OF HYPOTENSIVE DRUGS

It was shown earlier that the action of hypotensive drugs on the blood pressure depends on the excitability of the posterior hypothalamus. Moreover, stimulation of the hypothalamus with threshold currents which did not significantly alter the blood pressure diminished the hypotensive action of acetylcholine and related substances (see Fig. 5). It therefore seemed obvious that suprathreshold stimuli which by themselves exerted a pressor action would counteract even more effectively this hypotensive action, and experiments confirmed this

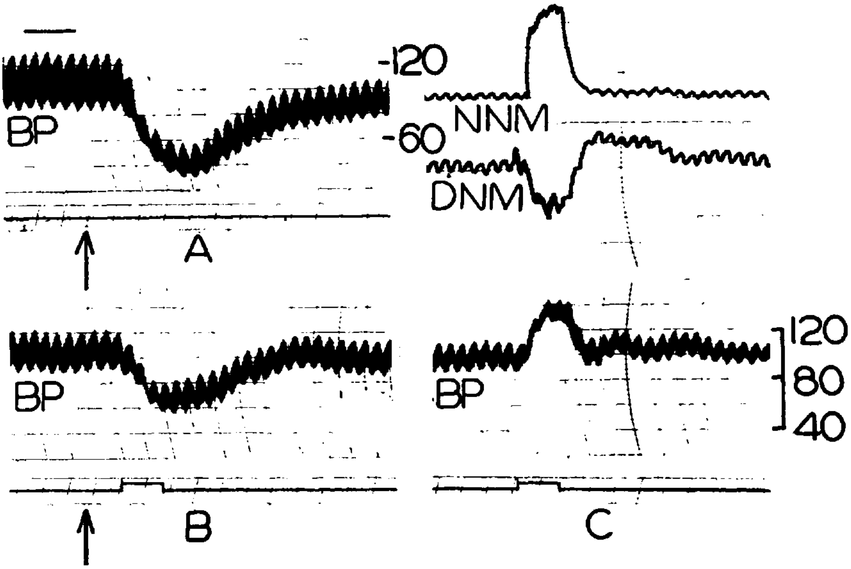

*Figure 67.* Interaction of hypothalamic stimulation, which causes a sympathetico-adrenal discharge in the control (*C*) and acetylcholine. Note that as a result of the interaction (*B*) the blood pressure fall is lessened and the return of the blood pressure to the control level is accelerated.

*A*. 5 gammas of acetylcholine (arrow). *B*. 5 gammas of acetylcholine with hypothalamic stimulation (signal magnet) as in *C*. *C*. Hypothalamic stimulation (2 v., 207 pps, 0.8 ms., 10 sec.).

conclusion. For reasons which will become clear in the later discussion of the interpretation of the mecholyl test under conditions of emotional excitement, the relation of hypotensive drug action to states of sympathetico-adrenal discharge was tested with special care. In one group of experiments hypothalamic stimuli that elicit a sympathetico-adrenal discharge were applied at the moment when the blood pressure began to fall following the injection of a hypotensive drug. As Figure 67 shows, the hypotensive action was greatly diminished under these conditions.

Similar results were obtained when the action of hypotensive drugs was tested in states of increased sympathetic or sympathetico-adrenal discharges resulting from asphyxia or occurring when air was readmitted after a period of asphyxia. From these experiments it may be concluded that states of increased central sympathetic or sympathetico-adrenal discharges counteract effectively the hypotensive action of mecholyl, acetylcholine, and histamine regardless of whether these states result from direct excitation of the hypothalamus through electrical currents or from changes in the internal environment (asphyxia).

## C. THE HOMEOSTATIC ACTION OF ADRENOMEDULLARY SECRETION AND ITS SIGNIFICANCE FOR THE ACTION OF MECHOLYL

The relation between the neurogenic and the hormonal (adrenomedullary) components of a central sympathetic discharge has thus far been discussed with respect to the conditions which lead to such a discharge. It was recognized that on mild stimulation partial sympathetic (neurogenic) discharges prevail and that only stronger stimulation will activate the sympathetic system as a whole and evoke the adrenomedullary component. Since the adrenomedullary secretion consists of noradrenaline and adrenaline and since these neurohumors in general exert effects on the target organs similar to those exerted by the stimulation of sympathetic nerves, Cannon (40) has assumed that the hormonal secretion serves as a reinforcing agent of the sympathetic discharge, particularly under conditions of emergency. This idea has received support from the recent work of Bonvallet *et al.* (23), who showed that the hormonal secretion contributes to the maintenance and prolongation of the sympathetic excitation of the cerebral cortex under conditions of sympathetic excitation.

Apparently contrary to this interpretation is our experimental finding that these neurohumors may oppose sympathetic action. It was shown earlier that the injection of adrenaline or noradrenaline leads to parasympathetic tuning, a condition in which the effect of sympathetic stimuli is greatly reduced or even reversed. Moreover, adrenaline and to a lesser degree noradrenaline may reduce sympathetic excitation by its blocking action on the synapses of the sympathetic ganglia. According to recent work (219), 0.001 mg. of adrenaline is sufficient to block the transmission through a sympathetic ganglion!

These observations pose two questions: (a) Does any evidence for this inhibitory action of the neurohumors exist when they are secreted from the medulla of the adrenal gland under strictly physiological conditions? Or, more specifically, during the hormonal discharge recorded by the contraction of the denervated nictitating membrane, is the neurogenic sympathetic discharge which acts on the normal nictitating membrane diminished or inhibited? (b) If such inhibition occurs, what is its influence on the hypotensive action of drugs like mecholyl and acetylcholine?

The answer to these questions is of importance for our understanding of homeostasis. Moreover, it will serve as an introduction to an important aspect of the physiology of the emotions.

That the latent period of the hormonal sympathetic discharge is relatively long is well known, and is illustrated in our Figures 64, 65, and 66 on hypothalamic stimulation. The neurogenically controlled contraction of the normal nictitating membrane therefore appears first —and most often at the very beginning of the period of stimulation of the hypothalamus—and is followed by the contraction of the denervated nictitating membrane. This sequence is likewise observed if, with or without hypothalamic stimulation, a sympathetico-adrenal discharge takes place during or immediately after a period of asphyxia. A close observation of these processes reveals that as the contraction of the denervated nictitating membrane develops, the contraction of the normal nictitating membrane ceases rather abruptly. That this relaxation of the normal nictitating membrane may be due to an inhibition of the neurogenic sympathetic discharge is supported by the fact that it appears very promptly if the hormonal secretion (indicated by the height of the contraction of the denervated nictitating membrane) is very large. Moreover, in experiments where intensive and prolonged hypothalamic stimulation caused a continuation of the neurogenic discharge into and even beyond the period showing contraction of the denervated nictitating membrane, it was found that the normal nictitating membrane relaxed temporarily during the hormonal discharge.

These results were confirmed in numerous experiments in which the pupils and nictitating membranes of unanesthetized cats were photographed under various experimental conditions. In these cats the superior cervical ganglion had been removed about ten days previously to ensure that the denervated pupils and nictitating membranes would have optimal sensitivity to secreted noradrenaline and adrenaline.

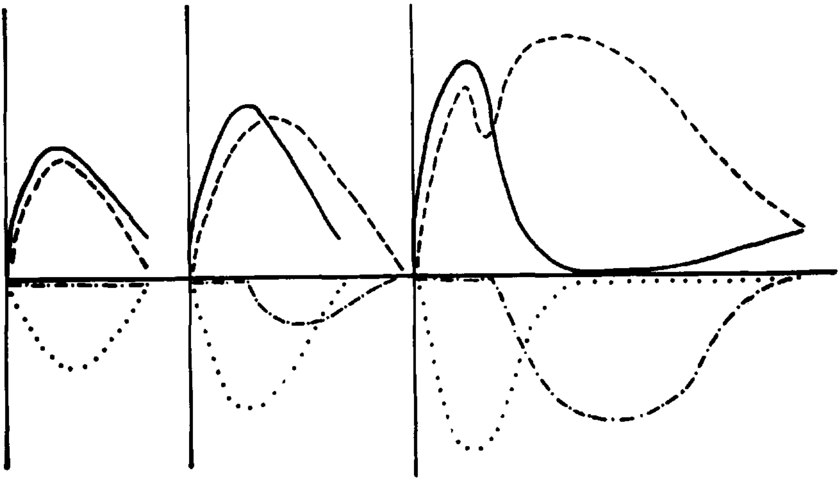

*Figure 68.* The effect of increasing excitation of sympathetic centers on pupillary dilatation and contraction of the nictitating membranes. Note that with mild excitation (left section) the normal pupil dilates and the normal nictitating membrane contracts while the denervated nictitating membrane remains unchanged. With moderate excitation (middle section) and with strong excitation (right section) the adrenomedullary secretion causes an excitation of the denervated structures. If the secretion is considerable as in the right section the normal nictitating membrane is inhibited and the normal pupil constricts while the denervated structures show maximal excitation.

Solid line = Normal pupil. Broken line = Denervated pupil. Dotted line = Normal nictitating membrane. Broken line with dots = Denervated nictitating membrane. Abscissa = Time. Ordinate = Degree of dilatation of the pupils upwards and of contraction of the nictitating membrane downwards from the abscissa.

Figure 68 illustrates schematically the effects of stimulation of varying degrees of intensity on the pupils and nictitating membranes. Mild stimuli, regardless of whether they affect the autonomic system reflexly (for instance, nociceptive stimuli) or directly (electrical stimulation of the posterior hypothalamus), cause a partial sympathetic discharge, apparent in the dilatation of the normal (and the lesser dilatation of the denervated) pupil* and in the contraction of the normal nictitating membrane. There is no contraction of the denervated nictitating membrane (left section of the figure). As the stimulus increases in intensity, the dilatation of the normal pupil and the contraction of the normal nictitating membrane increase in magnitude and speed. During the first few seconds of the response the behavior of the denervated structures does not change, but a little later the denervated pupil continues to dilate while the normal pupil begins to contract, and this dilatation is accompanied by a slight contraction of the denervated nictitating membrane (middle section). Finally, on strong stimulation the dilatation of the normal pupil and the contraction of the normal nictitating membrane become maximal. During this phase the dilatation of the denervated pupil is less than that of the normal, and again there is no contraction of the denervated nictitating membrane. Later, however, a dramatic change occurs: while the normal pupil contracts rapidly, the denervated pupil dilates maximally (paradoxical pupil, 3). This paradoxical reaction is accompanied by a maximal contraction of the denervated nictitating membrane while the normal nictitating membrane relaxes. This second phase may persist for one or more minutes (right section of Fig. 68).

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* On the nature of the pupillary dilatation see item 94, Chapter 12.

These observations show that mild degrees of sympathetic excitation involve the neurogenic mechanism, whereas stronger degrees call forth in addition the adrenomedullary secretion. As long as the adrenomedullary secretion is small (indicated by a minimal contraction of the denervated nictitating membrane), the neurogenic response is not interfered with, and even maximal pupillary and nictitating membrane reactions may occur on the normal eye. If, however, the adrenomedullary secretion * becomes large, the normal pupil contracts and the normal nictitating membrane relaxes. The observations suggest strongly that the adrenomedullary secretion does not reinforce the effects of sympathetic discharges, but actually inhibits them.

The validity of this conclusion was tested by the determination of the excitability of the sympathetic centers during a marked adrenomedullary secretion. If it is correct that this secretion inhibits the autonomic centers, the responsiveness of the hypothalamus during adrenomedullary secretion will be less than under control conditions. Figure 69 illustrates a pertinent observation. When air was readmitted after a period of asphyxia of 75 seconds, a contraction of the denervated but not of the normal nictitating membrane followed (*A*). When during the phase of postasphyxial adrenomedullary secretion the

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* The contraction of the denervated nictitating membrane and the paradoxical pupil are abolished after ligation of the adrenal veins unless excessive degrees of stimulation are employed (224). Concerning older investigations on the delayed secretion of adrenaline following hypothalamic stimulation, see item 18.

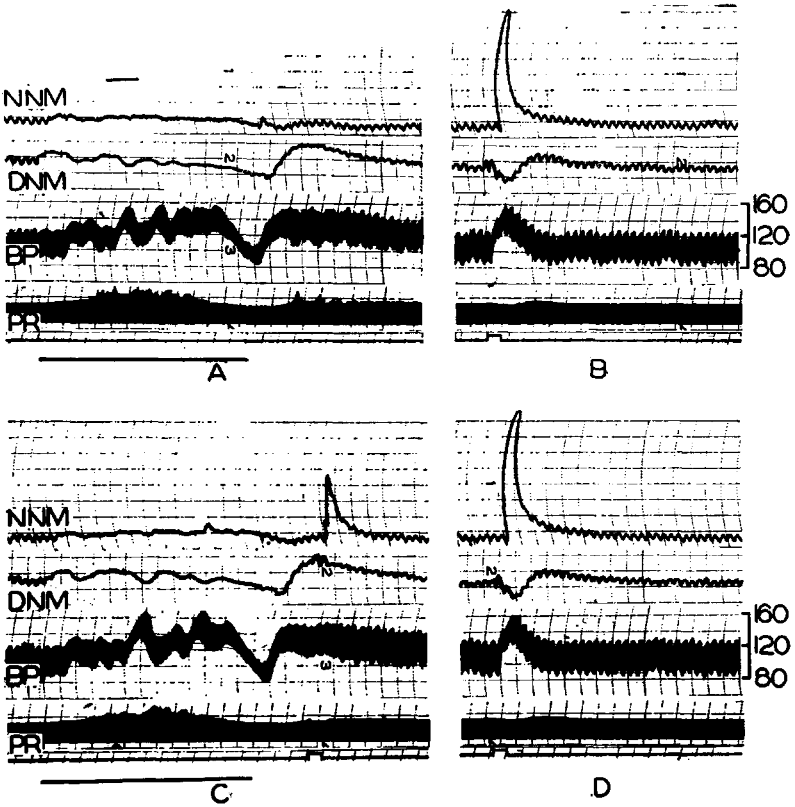

*Figure 69.* The effect of hypothalamic stimulation in the post-asphyxial condition during adrenomedullary secretion indicated by the contraction of the denervated nictitating membrane (*A*). Note that during this phase the sympathetic response (indicated by the innervated nictitating membrane) is decreased (*C*).

*A*. 75 seconds asphyxia (horizontal line). *B*. Left posterior hypothalamic stimulation (2.5 v., 99 pps, 1.6 ms., 5 sec.). *C*. 75 seconds asphyxia with *B* stimulus after readmission of air. *D*. Same as *B*.

hypothalamus was stimulated (*C*), the sympathetic effect was greatly reduced from that seen under control conditions (*B*, *D*). This reduction is evident from the lessened contraction of the normal nictitating membrane and from the failure of the stimulus to evoke a pressor response.

Experiments with hypotensive drugs confirm the fundamental differentiation between conditions in which the sympathetic neurogenic discharge dominates and those which involve chiefly a sympathetic hormonal, that is, an adrenomedullary discharge. Thus the hypotensive action of acetylcholine is less during the sympathetic discharge prevailing in a brief period of asphyxia (Fig. 70*B*) than during the control period (Fig. 70*C*). If, however, the action of hypotensive drugs is tested under conditions in which chiefly a large adrenomedullary secretion takes place, the results are quite different. As Figure 70 shows (compare *A* and *C*), the hypotensive action of acetylcholine is greatly aggravated during the phase of postasphyxial adrenomedullary secretion and results in a prolonged period of hypotension. Such a postasphyxial hypotension does not occur after a similar period of asphyxia if acetylcholine is not administered. Hence, the responsiveness of the hypothalamus to direct stimulation and the reaction of the blood pressure to hypotensive drugs undergo parallel changes during the various types of sympathetic and adrenomedullary discharges. Since hypotensive drugs elicit reflexly sympathetic discharges which

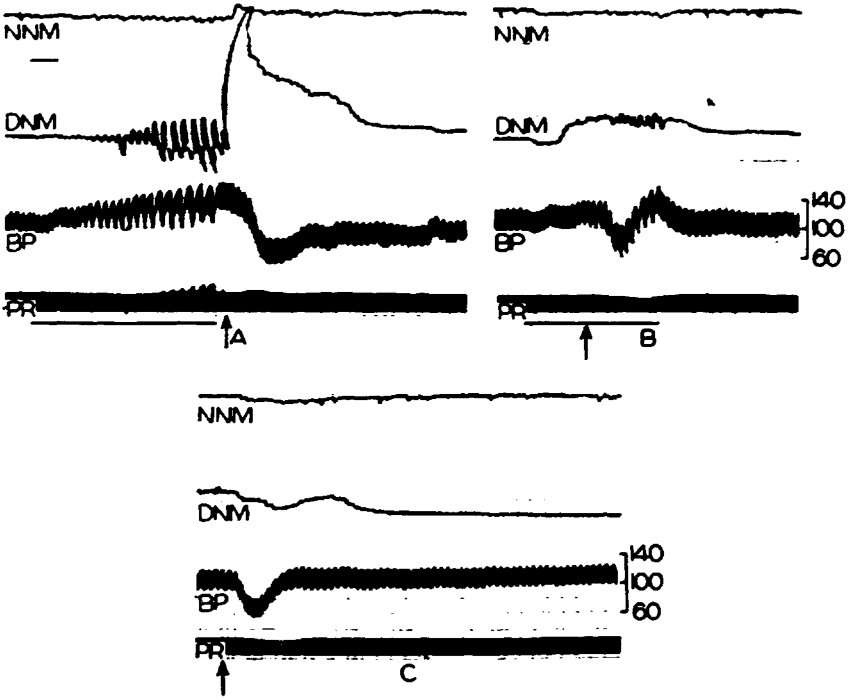

*Figure 70.* The effect of acetylcholine during and after asphyxia. The figure shows in *A* that the hypotensive action of acetylcholine is aggravated in the post-asphyxial state while a strong adrenomedullary secretion occurs, whereas it is lessened during asphyxia (*B*).

*A*. 95 seconds asphyxia (horizontal line) with 10 gammas of acetylcholine (arrow) in air. *B*. 55 seconds asphyxia with 10 gammas of acetylcholine at 25 seconds (during asphyxia). *C*. 10 gammas of acetylcholine.

determine the degree and duration of hypotension which they produce, it may be said that a dominance of neurogenic sympathetic discharges is associated with increased reactivity of the posterior hypothalamus to direct and reflex stimulation, whereas in states of dominance of the adrenomedullary secretion the responsiveness of the posterior hypothalamus to direct and reflex stimulation is greatly reduced.

## D. NORADRENALINE, ADRENALINE, AND THE ACTION OF HYPOTENSIVE DRUGS

The action of hypotensive drugs under various forms of sympathetico-adrenal discharges having been discussed, it remains to be

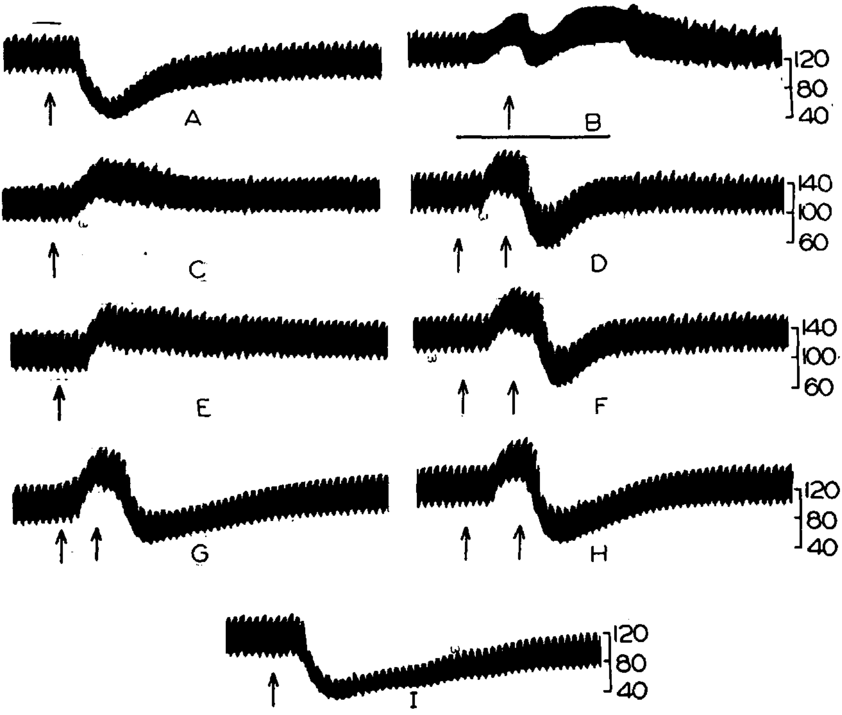

*Figure 71.* The effect of acetylcholine and mecholyl during a rise of the blood pressure induced by noradrenaline or adrenaline. Note that the hypotensive action is accelerated whereas it is greatly decreased when a hypotensive drug is administered during asphyxia (*B*).

*A.* 10 gammas of acetylcholine i.v. (arrow). *B.* 60 seconds asphyxia (horizontal line) with 10 gammas of acetylcholine (arrow) at 15 seconds. *C.* 5 gammas of noradrenaline. *D.* 5 gammas of noradrenaline (first arrow) with 10 gammas of acetylcholine (second arrow). *E.* 5 gammas of adrenaline. *F.* 5 gammas of adrenaline (first arrow) with 10 gammas of acetylcholine (second arrow). *G.* 5 gammas of noradrenaline (first arrow) with 1 gamma mecholyl (second arrow). *H.* 5 gammas of adrenaline (first arrow) with 1 gamma mecholyl (second arrow). *I.* 1 gamma mecholyl (arrow).

investigated how the action of these drugs is modified when they are injected after the blood pressure has been raised through adrenaline or noradrenaline.

The hypotensive drugs were injected at the moment when the pressor effect of noradrenaline and adrenaline was approximately at its maximum. In the tests shown at *D* and *F* of Figure 71, the fall of the blood pressure due to acetylcholine was slightly greater and more rapid than in the control test, shown at *A*, a result clearly indicating that the parasympathetic tuning due to noradrenaline or adrenaline creates effects which are exactly opposite to those prevalent when a rise of the blood pressure results from hypothalamic excitation or asphyxia. To show the fundamentally different behavior induced by these two sets of conditions, a record is included from a test in which the acetylcholine was applied during asphyxia (*B*) in the same animal. In this test the hypotensive action of acetylcholine was minimal. Similar results were obtained with mecholyl, the hypotensive action of which was likewise increased when it was applied during a noradrenaline- or adrenaline-induced rise of the blood pressure. The experiments suggest that the injection of adrenaline and noradrenaline through parasympathetic tuning aggravates slightly the hypotensive action of acetylcholine and mecholyl.*

## E. FACTORS ALTERING THE RELATIVE DOMINANCE OF NEUROGENIC SYMPATHETIC AND HORMONAL (ADRENOMEDULLARY) DISCHARGES

The preceding pages have shown that the two components, the neurogenic and the hormonal, which constitute the sympathetico-adrenal discharge influence the reactivity of the autonomic nervous system in opposite manners. During a neurogenic discharge (with or without minimal adrenomedullary secretion) the sympathetic system shows an increased responsiveness to direct and reflex stimulation, whereas during a marked adrenomedullary secretion the sympathetic reactivity is decreased greatly. An investigation of some of the influences that alter the ratio of the neurogenic and hormonal components of the sympathetico-adrenal discharge seems important. This ratio is referred to as the neurogenic-adrenomedullary quotient, or as N/A.

In 1951 it was shown (126) that a diminution of the N/A ratio in response to nociceptive stimuli occurs in chloralose or barbiturate anesthesia. The pupils and nictitating membranes of the cat served as indicators. Mild nociceptive stimuli evoked a greater pupillary dilatation of the normal than of the denervated eye and a contraction of the normal but not of the denervated nictitating membrane in the waking animal. In anesthesia, however, the denervated pupil and nictitating membrane reacted more than the normal structures to such stimuli. These experiments were confirmed in recent work in which it was noted that marked reactions to nociception of the denervated structures may occur in the absence of any reaction of the normal eye.

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* It is obvious that the success of the experiments depends on the excitability of the centers of the autonomic system. If these centers are depressed in deep anesthesia, the peripheral excitatory action of adrenaline on the heart and of noradrenaline on the blood vessels prevails and counteracts the hypotensive effect of acetylcholine or mecholyl. These latter effects seem to account for the fact that the hypotensive action of acetylcholine in noradrenaline tuning is perhaps shorter than in the control test.

This reversal may be present in anesthesia even in the absence of any stimulation. Whereas in the waking cat the normal nictitating membrane is always in a certain degree of contraction and the normal pupil wider than the denervated pupil, a contraction of the denervated nictitating membrane and a dilatation of the denervated pupil may gradually develop as a state of anesthesia is induced.

If in an awake cat a tracheal cannula inserted previously is obstructed, a strong sympathetic reaction of the normal pupil and nictitating membrane occurs. If this obstruction is brief, the sympathetic reaction is confined to the normal eye; if it is prolonged, the first reaction is followed by a maximal response of the denervated eye to the adrenomedullary secretion. In moderate and deep anesthesia the neurogenic effect becomes delayed and lessened while the adrenomedullary effect persists. Finally a state is reached in which only the denervated structures respond to the asphyxial condition.

These observations suggest that the neurogenic component is more easily affected by a lowering of the excitability of the central nervous system than the hormonal component. This inference is confirmed by the following groups of experiments, which likewise involved conditions leading to a reduction of central nervous excitability:

1. When in a lightly anesthetized animal a series of asphyxias (60–85 seconds) were performed, excitability of the central nervous system decreased. At the same time the sympathetico-adrenal response to asphyxia was altered. The contraction of the normal nictitating membrane occurred no longer, whereas the denervated nictitating membrane retained its response to asphyxia or even increased it: the N/A quotient was lessened.

2. As will be shown in the next chapter, curare-like substances reduce the excitability of the posterior hypothalamus and, as the changes of the EEG reveal the degree of cortical excitation. The effect of curarization on the N/A quotient was therefore investigated, the action of a given period of asphyxia on the nictitating membranes serving as a

test of the responsiveness of the sympathetic system. Here again a lowering of the N/A quotient occurred as in the anesthesia experiments.

The observations just described illustrate changes of the N/A quotient which are based on the contractions of the nictitating membranes. They were confirmed in similar experimental conditions with the pupils as indicators. In view of the fact that pupils and nictitating membranes are important indicators of the state of wakefulness, in which the hypothalamus plays a decisive role, it was thought that variations in hypothalamic excitability would alter the N/A quotient in response to certain standard stimuli. The following experiments seem to bear out this contention.

When asphyxia, applied for a certain duration, produced a neurogenic and an adrenomedullary response, the former was easily abolished by the injection of a minute amount of pentothal into the posterior hypothalamus, but the adrenomedullary response was retained. By this injection the N/A quotient, estimated on the basis of the contraction of the normal and denervated nictitating membranes, was likewise altered in response to stimulation of the posterior hypothalamus. The change in the N/A quotient was best shown if hypothalamic stimuli of different intensities were applied before and after the intrahypothalamic injection. The reduction of hypothalamic excitability by pentothal appeared as a greater reduction of the normal than of the denervated membrane. A stimulus which, after the injection, still failed to produce a contraction of the normal nictitating membrane as great as that produced by a weaker stimulus before the injection was able to produce a contraction of the denervated membrane as great as or even greater than that produced under control conditions.

Finally, it was noted that the N/A quotient was raised—i.e., that the neurogenic response was more intensified than the adrenomedullary response—when the hypothalamic excitability was increased by the injection of metrazol into the posterior hypothalamus. This effect was particularly impressive if anoxia was chosen as the test stimulus. Then it was seen that under control conditions only the denervated nictitating membrane showed a contraction in response to anoxia but after injection the normal nictitating membrane reacted likewise.

From these investigations it may be concluded that the ratio of the neurogenic to the adrenomedullary response under various experimental conditions depends on the excitability of the central nervous system in general and on that of the posterior hypothalamus in particular: with rising sympathetic hypothalamic excitability the N/A quotient increases.

## F. INTERPRETATION

The first group of experiments showed that with increasing excitation of the sympathetic autonomic centers, a partial sympathetic excitation is converted into a complete sympathetico-adrenal discharge. This statement is based on the fact that the milder forms of stimulation elicit a contraction of the normal but not of the denervated nictitating membrane, whereas both structures react to more intensive stimulation. Redgate and Gellhorn (259) have shown that hypothalamic stimulation liberates noradrenaline and that asphyxia liberates adrenaline from the adrenal medulla. It may, therefore, be assumed that when asphyxia was employed in the experiment described, the medullary secretion consisted largely of adrenaline, whereas in the absence of asphyxia the direct and reflex stimulation of the sympathetic centers led to a medullary secretion consisting chiefly of noradrenaline. Since both types of adrenomedullary secretion come into being as the degree of central excitation increases, it is obvious that they are associated with strong sympathetic discharges, as indicated by the acceleration of the heart rate and the rise of the blood pressure. It is, therefore, not surprising to find that the hypotensive action of mecholyl and related drugs is greatly diminished under these conditions.

In addition, the investigations have shown that the autonomic nervous system reacts quite differently when secretion or injection of adrenaline or noradrenaline occurs with little or no neural discharge. The reason for this difference is that the secretion from the medulla occurs ordinarily in association with strong neurogenic sympathetic discharges. In these circumstances the autonomic nervous system is tuned sympathetically and the hypotensive action of mecholyl is minimized. On the other hand, the injection of the neurohumors (adrenaline and noradrenaline) leads to a parasympathetic tuning of the autonomic nervous system and consequently to an aggravation of the hypotensive action of mecholyl and similarly acting drugs. Similarly, if the adrenomedullary secretion occurs in large quantities, as for instance in the postasphyxial state, the neurohumors reduce sympathetic excitability and the transmission through autonomic ganglia. It is suggested that if the secretion is accompanied by a rise of the blood pressure, the parasympathetic tuning through baroreceptor reflexes plays a role in reducing sympathetic excitability in addition to the direct blocking action of the neurohumors on synaptic transmission. Since Malméjac *et al.* (227-230) found that adrenaline inhibits the centers which regulate adrenomedullary secretion in minimal concentrations which do not raise the blood pressure, it is suggested that this blocking action plays an important role in strictly physiological conditions. This blocking action accounts also for the failure of synaptic transmission in circulatory shock (253). The bearing of these results on the concept of homeostasis will be discussed in Chapter 13.

A final group of experiments should be briefly evaluated. It was shown that the ratio of the neurogenic discharge (N), estimated from the contraction of the normal nictitating membrane, and the adrenomedullary discharge (A), estimated from the contraction of the denervated nictitating membrane,* is not constant, but depends on the state of excitability of the central nervous system. Anesthesia, repeated anoxia, and asphyxia reduce the N/A quotient, and a similar effect is produced by the deterioration of the central nervous reactivity as the result of prolonged excitation. This result is observed regardless of whether the sympathetico-adrenal discharge is produced by direct stimulation of the hypothalamus or reflexly (through nociceptive stimuli) or through a combination of reflex and central stimuli as in asphyxia. Since it is well known that anesthesia, anoxia, and asphyxia alter cortical and diencephalic processes more than those functions which are controlled by the lower brain stem, it was thought that the neurogenic component of the sympathetico-adrenal discharge would depend chiefly on diencephalic and cortical processes, in contrast to the adrenomedullary secretion, thought to depend primarily on the medulla oblongata. In support of this idea may be cited three groups of facts:

1. Houssay and Molinelli (176) state that the adrenomedullary secretion is elicited more effectively by stimulation of the medulla oblongata than by hypothalamic excitation.

2. The neurogenic indicators in our experiments (the nictitating membrane and the pupil) can be activated by electrical stimulation of the cerebral cortex (see item 87 for the literature). Another neurogenic sympathetic effect, the palmar sweating reaction, which is also closely related to attention and awareness, is thought to depend on the cerebral cortex (51). On the other hand, adrenomedullary secretion has not been elicited by stimulation of the cerebral cortex. On the contrary, the release of the brain stem from cortical control increases adrenomedullary secretion to a given stimulus (17).

3. According to the observations reported in this chapter, the N/A quotient is lowered when the excitability of the posterior hypothalamus is lowered by the injection of barbiturates into this structure. The lowering of this quotient is chiefly based on the diminution (or disappearance) of the neurogenic response. Inasmuch as the state of

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* Or by the dilatation of the denervated pupil.

the excitability of the cortex is codetermined by the condition of the posterior hypothalamus, it is understandable that a diminution of hypothalamic excitability may lead to a loss of certain cortical sympathetic reactions.

The alteration of the N/A quotient in different conditions in response to stimulation of the autonomic centers is of fundamental importance, since, as we have seen, the tuning of the autonomic nervous system is altered by the neurogenic and the adrenomedullary component in opposite manners. The neurogenic response leads to sympathetic tuning; the adrenomedullary secretion, to a damping of sympathetic centers and to parasympathetic tuning.

CHAPTER 4

# THE TONE OF THE SKELETAL MUSCLES IN ITS RELATION TO THE EXCITABILITY OF THE HYPOTHALAMUS AND THE EMOTIONS

THE studies of the last few decades have furnished many examples of the interrelation between the autonomic and somatic nervous systems. For the present discussion, which is concerned with the tone and activity of the striated muscles, the observations showing that the excitation of autonomic centers is associated with significant changes of the skeletal muscles are of importance. They are based on three sets of experiments:

1. Variations in the pressure of the carotid sinus caused marked changes in behavior and in muscle tone. When the pressure was raised, the unanesthetized animals became quiet, reacted less to environmental stimuli, and had a tendency to fall asleep. A fall of the intrasinusal pressure caused an increase in psychomotor activity and led to increased muscle tone and even to convulsions (197). These alterations in the state of the skeletal muscles were accompanied by corresponding changes in the intensity of the knee jerk in response to a standard stimulus (288). Further experiments (129, 130) showed the applicability of these studies to convulsions: a rise of the intrasinusal pressure, produced by mechanical or pharmacological means, caused a decrease of convulsions whereas a fall of this pressure had the opposite effect. These effects were abolished by denervation of the sino-aortic area.
2. Direct stimulation of various parts of the diencephalon with electrical currents in the awake cat established likewise evidence of the interrelation of autonomic and somatic phenomena. Stimulation of the posterior part of the hypothalamus (and some adjacent areas) resulted in sympathetic effects which were associated with a state of increased reactivity of the motor system. Contrariwise, the stimulation of the anterior hypothalamus leading predominantly to parasympathetic symptoms was accompanied by a lessened reactivity of the neuro-muscular system (151, 153). If we consider the fact that the rise of the intrasinusal pressure leads to parasympathetic discharges and the fall of this pressure to sympathetic discharges, the work listed in para-

graphs 1 and 2 may be summarized in the following way: The direct excitation of the hypothalamus or the reflex excitation of sympathetic centers through their release from the antagonistic action of the baroreceptors of the sino-aortic area is associated with an increased excitability of the motor system,* whereas the direct or the reflex activation of the parasympathetic system is accompanied by a marked loss of tone in the skeletal muscles and in some instances by a state of adynamy (150).

3. Stimulation of the gyrus cinguli resulted in autonomic and somatic effects (133, 285, 309). The autonomic effects were in part parasympathetic (fall of the blood pressure, slowing of pulse rate) and in part sympathetic (rise of the blood pressure, piloerection). These effects were associated with a powerful inhibition of movements, due to impulses conveyed from the cingular gyrus to the medial reticular formation of the pons. The syndrome of sympathetic excitation in combination with an inhibition of motor activity reminds one of the phenomena which accompany extreme fear and terror. The observation that ablation of this area leads to the loss of fear in experimental animals supports this interpretation.

In order to gain further insight into the relation between muscle tone, the hypothalamus, and emotional excitement, investigations were undertaken on the role of proprioception in diencephalic functions.

## A. PROPRIOCEPTION AND THE EXCITABILITY OF THE HYPOTHALAMUS†

It has been emphasized elsewhere (89, 91, 116, 117, 119) that motor functions are intimately related to proprioception. Voluntary movements are practically abolished after the elimination of proprioception through section of the dorsal roots, and movements elicited by stimulation of the motor cortex are greatly modified by proprioceptive impulses. The importance of proprioceptive impulses for hypothalamic function will be discussed in Chapter 7 in more detail. Suffice it to say here that proprioceptive impulses increase the activity of the hypothalamus in general and of the posterior hypothalamus in particular and contribute to the tonic discharges from the hypothalamus via the diffuse thalamic system to the cerebral cortex. Since the chief function of this system is the maintenance of alertness, it may be assumed that proprioceptive impulses play an essential role in this respect. The assumption is supported by Kleitman's experiments (194) on the prolongation of the period of wakefulness. This prolongation depended entirely on proprioception. Whereas wakefulness could be maintained in sitting or standing position, sleep occurred as soon as the experimental subjects were allowed to recline. The finding (255, 256) that lesions of the posterior hypothalamus are associated with symptoms of catatonia in which the limbs can be brought into awkward positions for long periods of time indicates likewise that proprioceptive regulation depends greatly on the hypothalamus.*

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* The centrally induced effects are dominant and are not significantly altered by the sino-aortic homeostatic reflexes evoked secondarily as the blood pressure rises.

† Unpublished experiments in collaboration with E. S. Redgate and H. M. Ballin.

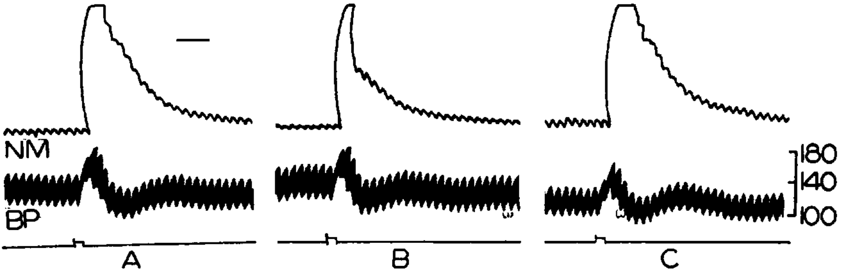

*Figure 72.* The effect of anectine on the excitability of the hypothalamus. Note that the sympathetic effect of the hypothalamic stimulation as indicated by the duration of the contraction of the nictitating membrane is reversibly decreased.

Stimulation of the posterior hypothalamus, 2 v., 207 pps, 0.8 ms., 3 sec. *A.* Control stimulus. *B.* Same stimulus 55 seconds after 1 mg/Kg anectine i.v. *C.* Same stimulus 10 minutes later.

A striking demonstration of the importance of proprioceptive impulses for the maintenance of hypothalamic excitability was obtained through a study of the action of curare-like substances. Intocostrin produced prolonged effects whereas anectin acted very briefly. In either case the responsiveness of the posterior hypothalamus to direct stimulation was greatly reduced, as indicated by the duration of the contraction of the nictitating membrane shown in Figure 72. In other experiments there was a progressive reduction in the contraction of the nictitating membrane and of the pressor response of the blood pressure, as the tone of the skeletal muscles diminished. It could also be shown that conditions which greatly increased hypothalamic sympathetic excitability in non-curarized animals had little or no effect after adequate curarization.

In view of the important role which the posterior hypothalamus plays in the maintenance of the activity of the cerebral cortex, it is not surprising that the EEG is markedly altered after the injection of these drugs. It was shown that in lightly anesthetized cats anectin produces large grouped potentials, as if a barbiturate had been injected intravenously or directly into the posterior hypothalamus. A few minutes later the original brain activity is restored. It is important to add that these fundamental changes occur without a fall of the blood pressure.

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* See also the recent work on the relation between the discharge rate of muscle spindles and the reticular system (135).

In other experiments cortical and hypothalamic potentials were recorded simultaneously. It was noted that the grouped potentials appeared also in the hypothalamus synchronously with those seen in various parts of the cerebral cortex. The experiments suggest that loss or diminution of proprioceptive impulses through curare-like substances reduces hypothalamic excitability and hypothalamic-cortical discharges.* This inference is confirmed by another group of experiments in which the effect of nociceptive stimuli on the cerebral cortex was studied under the influence of intocostrin. It will be shown later that these stimuli act on the hypothalamic-cortical system and that the excitability of the posterior hypothalamus plays a decisive role in the intensity and duration of their action on the cortex. In agreement with these findings it could be shown that the excitatory effect of nociceptive stimulation on the cerebral cortex was diminished after intocostrin had lowered the muscle tone and had thereby reduced the excitability of the posterior hypothalamus.†

Another indication of the profound influence which proprioceptive impulses exert on the posterior hypothalamus is the following observation: the amplitude and frequency of the convulsive discharges which had been produced experimentally by different means in the hypothalamus were markedly reduced by intocostrin. This effect was reversed when, some time later, the muscle tone returned.

* These observations are not incompatible with the findings of Smith (284) that the EEG in man is not altered after full curarization. In these tests the experimental subject was in a relaxed condition and curare did not diminish the proprioceptive impulses significantly, whereas in our experiments the EEG showed fast potentials of low amplitude, indicative of a state of cortical excitation which was greatly lessened through curare-like drugs. Shagass (278) points out a similar discrepancy between the effect of chlorpromazine on the EEG of man and cat (167), which seems to be based on the difference between the initial states of the brain.

† Certain clinical experiences appear in a new light on the basis of our experimental work. Anesthesiolgists claim that less anesthetic is required for a certain operation if it is carried out with the aid of curare-like drugs. The functional deafferentation which these drugs produce on the hypothalamus and which results in a state of lessened cortical excitability, as revealed by the EEG, may well account for the lessened anesthetic threshold.

## B. PROPRIOCEPTION AND THE EMOTIONS *

On the basis of the well-established significance of the hypothalamus for the emotions and the experiments, just described, showing that the diminution of proprioceptive impulses by curare-like substances diminishes hypothalamic excitability, it may be suggested that emotional reactivity is related to the tone of the striated muscles, which in turn determines the intensity of the proprioceptive discharge. In order further to clarify this relation, the following experiments were performed.

In one group the effect of hypothalamic stimulation was studied in awake cats in which hypothalamic electrodes had previously been inserted. In these animals it was confirmed that hypothalamic reactivity to electrical stimulation is lessened when through anectin the proprioceptive impulses have been diminished. Stimuli which before anectin produced a marked or maximal dilatation of the pupil and a contraction of the nicititating membrane evoked these and other sympathetic symptoms (piloerection) to a lesser degree after the muscle tone had been diminished by anectin. Moreover, cats which before the injection of the drug were quite alert appeared sleepy and returned to this state almost immediately after an arousal reaction had been produced by hypothalamic stimulation. In some instances aggressive tendencies, indicated by growling, hissing and spitting, and forward movements suggesting that the cat was ready to jump at the experimenter, disappeared, and there was a tendency for the cat to crawl into a corner (escape reaction?). A cat that after hypothalamic stimulation had previously bitten one of the observers reacted to the same or an even stronger stimulus mainly by walking forward a little and then turning to the back corner away from the experimenter. But there was no motor impairment of the masticatory muscles, since the cat bit vigorously on a rag held in front of the mouth. The tendency of previously aggressive cats to retire to the farthest corner even if pulled forward by the experimenter is noteworthy.

In another group of cats the behavior of the animals held on a long leash was studied before and after the injection of anectin. In their behavior toward the experimenter and also when confronted with a dog, the cats seemed to be more shy after anectin and to display a tendency to escape not present in the pre-injection control tests. Although these results could not be obtained regularly, a tendency to sleep and curl up in a corner and a lesser reaction to environmental stimuli were generally present.

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* Unpublished observations (100).

## C. EVALUATION

It was found that curare-like drugs, such as intocostrin and anectin, raise the hypothalamic threshold to electrical stimulation. These drugs also diminished the action of nociception on the hypothalamic-cortical system. In addition, experiments, not described above, showed that conditions, such as asphyxia, which raise the excitability of the posterior hypothalamus were less effective after intocostrin or anectin had been administered. The various effects of the drugs were reversible: the excitability of the posterior hypothalamus increased as the tone of the striated muscles returned. These drugs block the neuromuscular junction, the muscles relax, and consequently proprioceptive impulses, which have been shown to be powerful activators of the posterior hypothalamus, are abolished. As a consequence hypothalamic excitability is lessened, a change which finds its typical expression in the increase of grouped potentials in the hypothalamus. But this change of excitability does not remain confined to the hypothalamus itself; it is reflected also in the cortex,* in which grouped potentials appear likewise.

The behavioral changes seen after the administration of these curare-like drugs are in agreement with the lessened excitability and rate of discharge of the posterior hypothalamus. Bearing in mind that the posterior hypothalamus has a great influence on awareness (21) it is easily understandable that after the administration of curare-like drugs the responsiveness to environmental stimuli is lessened and a tendency toward sleepiness appears.† In response to a dog or to the experimenter who tried to tease the cat and also in its spontaneous behavior (in the absence of conspicuous changes of the external environment) the cat lost some aggressiveness and showed escape reactions. That these changes did not occur in each instance is perhaps not surprising, since the muscle tone and the reactivity of the posterior hypothalamus depending on it are certainly only one of many factors which play a role in the genesis of different types of emotion. Nevertheless, the loss of muscle tone and consequently of proprioception may represent at least a factor predisposing to fear. This idea is supported by the fact that the elimination of a cortical area which on stimulation causes sympathetic excitation and loss of muscle tone will produce "fearless" monkeys (309).

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* For a discussion of the hypothalamic-cortical system see Chapter 7.

† The effect of Jacobson's therapy (181) of progressive muscular relaxation in conditions of emotional disorders appears to be based, at least in part, on the acquired habit to relax the muscles and thereby to diminish proprioceptive impulses acting on the posterior hypothalamus.

A tentative application of this work to some forms of emotions suggests itself. Although action potential studies of skeletal muscles in man in different states of emotion are lacking, common observation seems to show that in the state of rage and also of resentment the tone of the skeletal muscles is augmented.* On the other hand, states of fear and terror appear to be associated with an inability to move and a loss of muscle tone. Moreover, it was observed that gastrointestinal activity is increased in resentment and diminished in fear (322, 323) and that the increased tone and activity of the gastrointestinal tract is associated with an increased tone of the skeletal muscles (247). It is not known to what extent the different somato-autonomic discharges which accompany fear and resentment are due to differences in diencephalic and in reflex discharges (from the viscera to the muscles and vice versa). Nevertheless, from the experiments reported in this chapter showing the importance of proprioceptive impulses for the reactivity of the posterior hypothalamus, it is inferred that in fear and terror the sympathetic diencephalic discharge is less than in rage and resentment. This inference has an important bearing on the reaction to mecholyl in these conditions on which Funkenstein (77, 78) reported, a question which will be discussed in Chapter 12.

The observation that curare-like substances modify emotional behavior is not to be construed as a support for the James-Lange theory of the emotions. Although the action of intocostrin and anectin concerns the neuromuscular function, these drugs act on central autonomic structures, such as the posterior hypothalamus, through the elimination of proprioceptive impulses. It may be added that this effect of the drugs is the only one with which we are concerned. The blocking action of curare on synapses requires much higher doses than were employed in this work (234).

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* Dickes *et al.* (57) showed recently that muscle tension is increased in states of anxiety.

## CHAPTER 5

# ON THE RELATION OF THE HYPOTHALAMUS TO THE VISCERA

THE tuning concept which played a central role in our investigations was derived from experiments involving the circulatory system. Thus it was shown that a reduction in the baroreceptor reflexes by an experimentally induced fall of the blood pressure (and thereby of the sino-aortic pressure) led to a sympathetic tuning, that is, to an increased sympathetic responsiveness to the stimulation of the posterior hypothalamus or the sciatic nerve. Similar effects of sympathetic tuning were produced by direct stimulation of the posterior hypothalamus or the sciatic nerve. The blood pressure and heart rate increased and in this condition the response of the vascular system (and of the nictitating membrane) to sympathetic stimuli was augmented.

In order to accomplish a state of sympathetic tuning, the tuning stimulus, regardless of its nature, must be able to produce a sympathetic effect on the target organ.* To determine the limits of the tuning processes in the organism becomes, therefore, of great importance. For this purpose a study was performed on the effect of the excitation of the posterior hypothalamus and the sciatic nerve on the state of the viscera. Although some experiments were also performed on the effect of lowering and raising the blood pressure (and thereby the sino-aortic pressure) by the use of acetylcholine, histamine, and noradrenaline, they are not reported because the action of the drugs on the target organs makes the distinction between their direct effect and the secondary one resulting from the sino-aortic reflexes rather hazardous.

The experiments discussed in this chapter will show that while some organs are in a state of sympathetic tuning, others, such as the bladder, may be in a state of increased parasympathetic responsiveness. This finding is of interest inasmuch as it shows the complexity of the

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NOTE: The basis of this chapter is unpublished work in collaboration with E. S. Redgate and H. M. Ballin.

* A tuning stimulus that may not lead to an overt response of a certain organ or tissue, for instance the nictitating membrane, may yet facilitate the effect of another (test) stimulus; but if the first stimulus is to accomplish a state of sympathetic tuning, it must produce a direct sympathetic effect on this organ *when applied at an adequate intensity.*

autonomic functions in the organism. In addition, it creates a physiological basis for an understanding of the effect of emotional stress on autonomic functions in certain groups of patients.*

In order to gain more insight into the autonomic reactivity of various organs, the parameters of stimulation of the posterior hypothalamus were varied widely while the blood pressure, heart rate, and the tone and activity of the gut and bladder were recorded.

## A. AUTONOMIC EFFECTS ON THE BLADDER AND GUT

In numerous experiments the activity of the bladder and duodenum was recorded, together with the blood pressure and heart rate, while sympathetic effects were produced by stimulation of the posterior hypothalamus or the sciatic nerve. In very lightly anesthetized cats the threshold of the bladder to hypothalamic stimulation was frequently noted to be much lower than that of the other structures recorded. Thus a stimulus that failed to alter the blood pressure and the tone and activity of the duodenum produced a contraction of the bladder. If the excitation was increased by increasing either the frequency or voltage of stimulation, the contraction of the bladder increased in amplitude and duration, and in the other structures sympathetic effects appeared, as indicated by a rise of the blood pressure, an acceleration of the heart rate, and a diminution in the amplitude of the contractions of the duodenum associated with a loss of tone. Such a typical effect is illustrated in Figure 73. It will be noted that the effects on the bladder and gut persisted beyond the period of stimulation. The contraction of the denervated nictitating membrane indicated that an adrenomedullary secretion was likewise produced. The effect on the viscera, however, was obviously not due to this secretion, since it occurred during, and the secretion after, stimulation. Moreover, similar effects were frequently recorded in the absence of a contraction of the denervated nictitating membrane.

If the intensity of stimulation was increased considerably, the adrenomedullary secretion was enhanced, and the effect on bladder and gut was fundamentally altered: both structures were inhibited. The inhibition coincided with the period of adrenomedullary secretion. A similar inhibition was produced by the injection of adrenaline or noradrenaline. It can hardly be doubted that in these circumstances the secretion accounts for the inhibition. The sensitivity of the bladder and gut to neurohumors, however, was unequal, since the duodenum often reacted to injected or secreted amounts of the neurohumors that were ineffective for the bladder.

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* See Chapter 9.

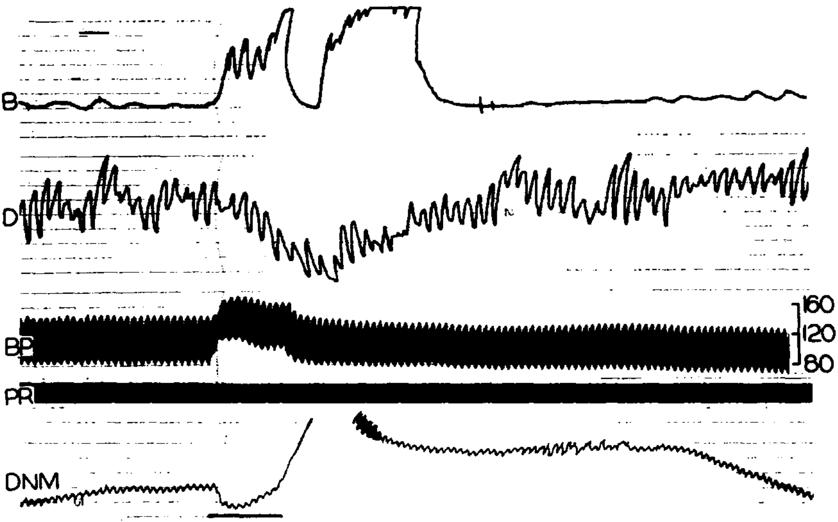

*Figure 73.* The effect of stimulation of the left posterior hypothalamus (indicated by the horizontal bar at the bottom) on bladder (*B*), duodenum (*D*), blood pressure, pulse rate, and denervated nictitating membrane. Note that the strong sympathetic excitation which causes a rise of blood pressure, inhibition of the gut, and adrenomedullary secretion (indicated by the denervated nictitating membrane) is associated with a parasympathetic excitation of the bladder.

Left hypothalamus is stimulated with 2.0 v., 99 pps, 0.8 ms. for 30 sec. Bar at left upper corner = 12 seconds.

Since the differential effect of hypothalamic stimulation on duodenum and bladder could be duplicated by appropriate stimulation of afferent nerves such as the sciatic, it may be said that through reflex stimulation of the autonomic nervous system or through direct stimulation of the hypothalamus some viscera (such as the bladder) may be in a state of greatly increased activity—that is, in an augmented parasympathetic state—while the blood pressure, heart rate, and the inhibited duodenum indicate increased sympathetic discharges. Obviously, the state of sympathetic tuning induced by powerful central or peripheral stimuli does not exist uniformly throughout the organism.

Similar results were obtained in experiments on the action of asphyxia. If the period of asphyxia was so brief that no adrenomedullary secretion occurred, sympathetic effects appeared in the blood pressure and heart rate and also on the gut (the last showing an inhibition of the tone and a diminution in the amplitude of the contractions), but the bladder remained unchanged. Only when the asphyxia led to a marked adrenomedullary secretion did an inhibition of the bladder and duodenum occur, together with marked sympathetic effects on the blood pressure and heart rate.

These experimental observations leave no doubt that conditions leading to considerable sympathetico-adrenal discharges impose a uniform pattern on the whole organism. But such a state is probably rather unphysiological, and characteristic of excessive stress. Under physiological conditions stimuli that exert sympathetic effects on the vascular system are found to have a strong parasympathetic action on other organs such as the bladder. These findings seem to be applicable to clinical conditions.

## B. THE HYPOTHALAMUS AND INTESTINAL ACTIVITY

Stimulation of the hypothalamus has been shown by numerous authors (307) to cause excitation or inhibition of the smooth muscle of the duodenum. The effect from the posterior hypothalamus was predominantly inhibitory, that from the anterior hypothalamus mainly excitatory. This distinction is, however, not clear cut, and the parameters of stimulation play an important part. In order to investigate further what the limits of the concept of tuning are, or, to express it differently and more specifically, in order to investigate whether centrally induced sympathetic discharges may be limited to certain organs while others are in a different autonomic state, various degrees of excitation were produced in the posterior hypothalamus by varying the voltage, frequency, duration of impulse, and stimulation time. The blood pressure, heart rate, and activity of the duodenum served as autonomic indicators.

If the posterior hypothalamus was stimulated with increasing voltage, signs of increasing sympathetic excitation appeared in the vascular system and the gut. As Figure 74 shows, the rise of the blood pressure and the inhibition of the duodenum increased in magnitude and duration. In addition, as noted in *B* and *C*, there was a "delayed excitation," which likewise increased with increasing excitation of the hypothalamus. This excitation appeared in the form of a greatly increased activity of the gut and often also in an increased tone (see Fig. 75*B*). It should be noted that this parasympathetic phase occurred long after the sympathetic excitation of the blood pressure and heart rate had passed.

Systematic experiments showed that the occurrence and the intensity of the delayed excitation of the gut are related to the degree of hypothalamic excitation. Regardless of whether the voltage, the duration of the impulse (square wave), the frequency, or the length of stimulation was increased, the delayed excitation occurred when the sympathetic excitation had reached a critical value. Moreover, the delayed excitation increased with further increase in the excitation of the hypothalamus. It is, therefore, established by these experiments that the excitation of the posterior hypothalamus which leads to marked and generalized sympathetic effects—they were not restricted to those recorded in Figures 73 to 75, but resulted also in a contraction of the nictitating membrane, piloerection, pupillary dilatation, sweating, etc.—may cause a considerable and often long-lasting parasympathetic excitation of the duodenum. Interesting as these observations are, particularly from the point of view of the autonomic physiology of the emotions, it must be admitted that they do not contradict the traditional ideas of the function of the sympathetic nervous system.

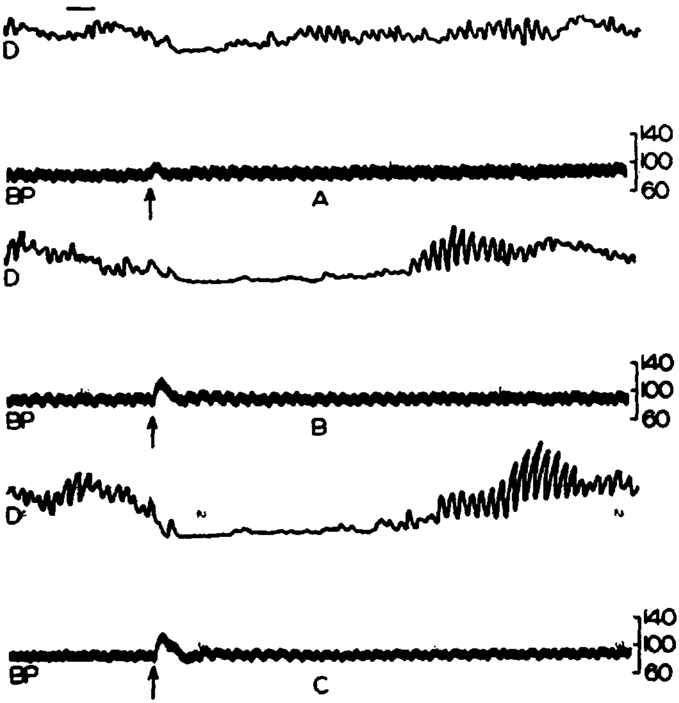

*Figure 74.* The effect of stimulation of the posterior hypothalamus on duodenum and blood pressure with increasing voltage. Note that the weakest stimulus (*A*) causes an inhibition of the gut whereas the stronger stimuli (*B*, *C*) cause an inhibition followed by an increase of the amplitude of the contractions and of the tone of the gut.

Hypothalamic stimulation. *A*. 1.0 v., 207 pps, 0.8 ms. for 3 sec. *B*. 1.5 v., 207 pps, 0.8 ms., for 3 sec. *C*. 2.0 v., 207 pps, 0.8 ms. for 3 sec. Bar at upper left = 12 seconds.

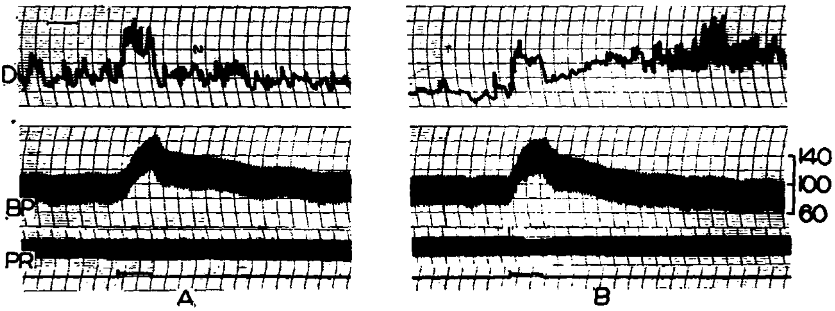

*Figure 75.* The effect of stimulation of the posterior hypothalamus on the autonomic balance of different organs. Note that a parasympathetic excitation of the gut is associated with sympathetic effects on the blood pressure and heart rate.

Stimulation of left posterior hypothalamus. *A*. 2.0 v., 99 pps, 0.8 ms. for 30 sec. *B*. 2.0 v., 207 pps, 0.8 ms. for 30 sec.

During the first phase of excitation (although greatly outlasting the period of stimulation and differing considerably in duration in various organs and systems *) only sympathetic effects were noted. The parasympathetic phase followed the sympathetic phase of gut activity, while the blood pressure, heart rate, and other organs (pupil and nictitating membrane) were in the resting state.

Another type of response is shown in Figure 75. This figure, in common with the previously discussed work, illustrates that the delayed excitation manifests itself after the degree of excitation has reached a certain level. Stimulation at a frequency of 99/sec was ineffective in this respect, whereas stimulation at 207/sec produced a delayed excitation of the duodenum characterized by an increase in tone and in amplitude of the contractions. In addition, this figure shows that *during* stimulation antagonistic autonomic effects appeared in the gut and in the vascular system. While the blood pressure rose (*A*, *B*) and the pulse rate increased (*B*), the tone of the duodenum increased in both tests. These experiments, just like those on the bladder previously described, show that following hypothalamic stimulation the type of autonomic activation of the gastro-intestinal tract may fundamentally differ from that of the vascular system.

Whereas in the experiments illustrated in the last figure a sympathetic vascular reaction was associated with a parasympathetic action on the gut, the opposite phenomenon was likewise observed. Thus a stimulation of the sciatic nerve (particularly with low frequencies) was found to elicit a typical parasympathetic reaction of the blood pressure but to have a sympathetic effect on the duodenum (loss of tone and diminution of the amplitude of the contractions).

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* Compare the brief duration of the pressor effect with the long period of inhibition of the gut in Figure 74.

Although in the majority of the experiments the excitation of the sympathetic nervous system induced reflexly or by stimulation of the posterior hypothalamus led to sympathetic effects on the gut, our studies show that sympathetic vascular effects may be associated with parasympathetic effects on gut (and bladder). Similarly, parasympathetic vascular effects may be associated with a sympathetic action on the gut. There was evidence, in some experiments, that baroreceptor reflexes were responsible for the deviation in the autonomic activation pattern of the gut; but this mechanism does not explain the reaction of the gut in other experiments in which parasympathetic or sympathetic effects were observed on the duodenum at a time when the blood pressure was unchanged. How complex the innervation pattern may be which follows hypothalamic stimulation is seen in Figure 76. During stimulation the blood pressure and heart rate were practically unchanged while the gut showed a large increase in tone and the respiration, after a brief delay, was augmented in frequency (phase *A*).*

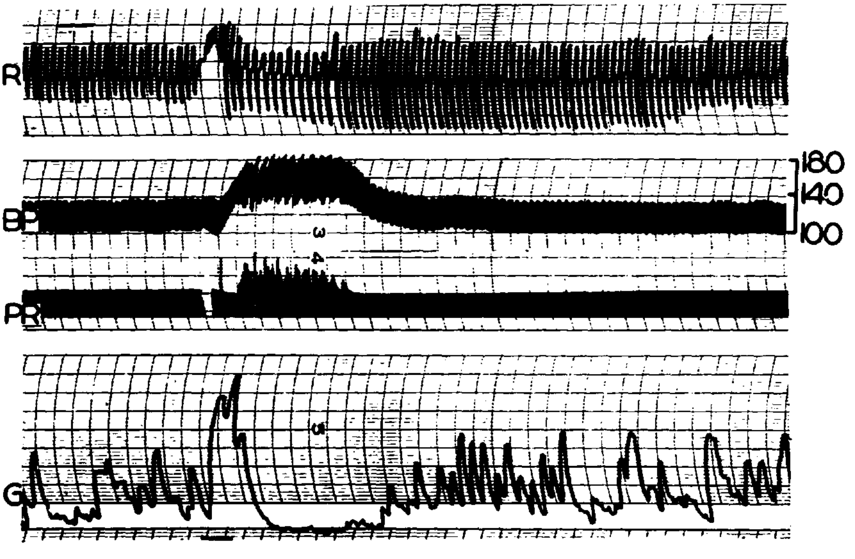

*Figure 76.* The effect of stimulation of the posterior hypothalamus (indicated by the horizontal bar at the bottom of the figure) on respiration, circulation, and activity of the gut. For explanation see the text. R = respiration.

Bar in the upper left corner = 12 seconds. The sciatic nerve was stimulated with a square-wave current, 3.0 v., 100 pps, 1 ms. for 10 sec.

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* This increased frequency of respiration is not clear in Figure 76 owing to reduction in size.

Then followed phase *B*, in which the blood pressure and heart rate increased while the tone of the gut remained high and the increased respiration persisted (now in amplitude and not in frequency). Phase *C* is characterized by the maintenance of an increased blood pressure, a reflex slowing of the heart, an inhibition of the respiration (diminished frequency), and a marked inhibition of the gut. While the blood pressure and heart rate returned to the control level in phase *D*, the respiration was increased in amplitude (and slightly in frequency) and the gut showed a delayed excitation. Finally, the control level was reached. The record shows that in all phases some parts of the body were in the trophotropic and others in the ergotropic state (Table 6). Whereas baroreceptor reflexes appear to be responsible for some reactions—e.g., the decrease in respiration and heart rate in phase *C*—they do not account for the behavior of the gut in phases *A* and *D*.

Table 6. An Analysis of Figure 76 in Terms of Ergotropic and Trophotropic Functions

| | Phase | | | |
|---|---|---|---|---|
| | A | B | C | D |
| Ergotropic | Respiration | Respiration<br>Blood pressure<br>Heart rate | Blood pressure<br>Duodenum | Respiration |
| Trophotropic | Duodenum | Duodenum | Respiration<br>Heart rate | Duodenum |
| Unchanged | Blood pressure<br>Heart rate | | | Blood pressure<br>Heart rate |

## C. EVALUATION

That a vigorous contraction of the bladder has been obtained on stimulation of the posterior hypothalamus is in agreement with the work of Ranson, Kabat, and Magoun (257). In their experiments this contraction was associated with a marked increase in the blood pressure and respiration and was obtained also after curarization. We made similar observations and showed in addition that an inhibition of the gut and adrenomedullary secretion may take place at the same time. Since elimination of the pelvic nerves (308) or section of the spinal cord above the second sacral level either completely or almost completely abolishes the effect of hypothalamic stimulation on the bladder, the parasympathetic nature of the hypothalamic action on the bladder seems well established.

In our experience the same syndrome may result from the reflex stimulation of afferent nerves. It is apparent that in one organ a state of parasympathetic excitation may exist and in other organs a state of sympathetic excitation as a result of the reflex or hypothalamic activation of the autonomic system.

Figure 75 illustrating the simultaneous occurrence of an increased tone of the gut and an increased blood pressure and accelerated heart rate on stimulation of the posterior hypothalamus—the one a parasympathetic, the other a sympathetic effect—is a further case in point. This experiment raises the question whether baroreceptor reflexes, during reflexly or hypothalamically produced variations of the blood pressure, may secondarily influence the autonomic state of the viscera.

Schweitzer (274, 275) observed that an increase of the pressure in the isolated carotid sinus resulted in a fall of the blood pressure, the quieting of the animal, an increase in the tone and activity of the gut, but also in a relaxation of the bladder. Apparently alterations in the sino-aortic pressure modify the autonomic state of the gastrointestinal tract (193) and the vascular system (blood pressure, heart rate) in the same manner, since, in the example given above, these viscera show a state of parasympathetic excitation, but the bladder behaves differently. Schweitzer says that the tone of the bladder does not depend on the baroreceptor reflexes but is related to the general state of activity of the animal. He notes also the great sensitivity of the bladder to tactile or acoustic stimuli in the intact animal and the loss of this sensitivity by decerebration. These observations suggest that the reactivity of the bladder depends to a large extent on the hypothalamus, which plays a decisive role in the state of psychomotor activity of the organism (153, 256). It is, therefore, of great interest that most of our preliminary experiments on the effect on the bladder of injecting pentothal intrahypothalamically showed a loss of tone and a decreased amplitude of the contractions; but more work is needed along these or similar lines.

Although the parallelism between the rise of the blood pressure and the tone of the duodenum, particularly during the period of stimulation (Fig. 75), suggests strongly that the rise of the tone of the gut involves the baroreceptor reflexes, other experiments (see Fig. 73) show clearly that the excitation of the sympathetic system (reflexly or at the hypothalamus) may lead to sympathetic effects on the blood pressure *and* the gut. Apparently, the baroreceptor reflexes were stronger than the sympathetic effects on the gut in the first case, whereas the reverse was true in the second case. Even in the second a sympathetic state was not generally dominant, since the bladder showed a vigorous and prolonged contraction. The parasympathetic effect on the bladder is obviously not related to changes in the blood pressure (and consequently in the pressure of the carotid sinus) and Schweitzer's work presents likewise no evidence for such a dependence. It is, therefore, concluded that a state of parasympathetic dominance in one organ and of sympathetic dominance in another organ occurs even under conditions which exclude baroreceptor reflexes. Records obtained under a variety of conditions of hypothalamic stimulation suggest that in all cases parasympathetic and sympathetic discharges are initiated. Depending on the site and the parameters of stimulation and also on the physiological state of the organs and tissues on which the autonomic discharges act, the autonomic balance may be influenced differently in different organs and also in the same organ at different times. This discrepancy in the autonomic state of various parts of the body is emphasized because of its clinical significance* and its importance for the concept of tuning. Apparently stimuli which induce a state of sympathetic tuning—for instance, through excitation of the posterior hypothalamus or through baroreceptor reflexes—may neither have a sympathetic effect on the gut nor produce a relaxation of the bladder.† In spite of this limitation, the fundamental laws of tuning modifying the responses of the blood pressure and the heart rate are important in view of the great role of circulation for the function of all organs, Moreover, it should be stressed that a state of sympathetic tuning affecting circulation and gut in a similar manner was often seen on direct or reflex excitation of the autonomic system. Conversely, a change of the autonomic balance to the parasympathetic side may occur in a large section of the organism. Thus an appropriate stimulation of the sciatic nerve may induce a fall of the blood pressure, a decrease in the heart rate, and an increase in the tone and activity of the duodenum.

Finally, it has been shown that stimulation of the posterior hypothalamus leads to a phase of delayed excitation of the gut which increases in degree and duration as the stimulus is increased in intensity. This parasympathetic phenomenon frequently occurs a considerable time after the sympathetic effects on heart and blood pressure have ceased, but it is directly related to the degree of the preceding sympathetic excitation. This tendency of a sympathetic discharge to be followed by a parasympathetic discharge is not specific for the gut. The parasympathetic induction discussed earlier shows a similar tendency for the blood pressure and heart rate. Only the magnitude and duration are different.*

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* See page 223.

† A relaxation of the bladder could theoretically occur through inhibition of the parasympathetic tone and also through sympathetic excitation (205). Most authors, however, agree that the sympathetic effect on the bladder is insignificant.

The fact that the parasympathetic delayed excitation of the gut increases in direct relation to the preceding sympathetic excitation is of great importance for the physiology of the emotions. It was emphasized in the preceding chapters that the responsiveness of the posterior hypothalamus to electrical stimulation (and presumably to emotional excitation) is enhanced by proprioceptive impulses. A diminution of these impulses was found not only to decrease the responsiveness of the hypothalamus to electrical stimulation but also to alter the N/A quotient:† the neurogenic discharge is lessened whereas the adrenomedullary discharge is increased. Let us add to these data the new finding about the relation between the delayed excitation and the intensity of hypothalamic excitation and remember that in fear the tone of the muscles (and therefore the degree of proprioceptive discharges) is apt to be low whereas it tends to be high in the state of resentment. According to Wolf and Wolff, states of anxiety and hostility are associated with parasympathetic, and fear with sympathetic effects on the gut (322, 323). It seems to follow that the former are, at least in part, an expression of the delayed excitation following a strong excitation of the hypothalamus, whereas the lesser neurogenic responsiveness of the hypothalamus in fear and the relatively greater role of the adrenomedullary secretion tend to intensify the inhibitory (sympathetic) action on the gut. The "downward" discharge from the hypothalamus may therefore be qualitatively different because of marked quantitative differences in the two forms of emotion under discussion.

* See p. 24.

† See Chapter 4.

CHAPTER 6

# RESPIRATORY REFLEXES AND THE HYPOTHALAMUS

A LARGE part of this monograph has been devoted to a study of vascular reactions in their dependence on the anterior and posterior divisions of the hypothalamus. In view of the fact that vascular and respiratory functions are intimately interrelated, it seems to be advisable to subject respiratory reflexes to a similar investigation. Such an investigation should have two goals: (a) to determine whether the principles underlying hypothalamic control of vascular relations are applicable to the area of respiratory reflexes; (b) to investigate the possibility of using respiratory functions as indicators of the state of the hypothalamus.

That respiration is altered by stimulation of the hypothalamus is well established. Stimulation of the posterior hypothalamus (chiefly of the lateral hypothalamic area) elicits, in addition to the rise of the blood pressure and other sympathetic effects, an increase in the rate and depth of respiration. On the other hand, stimulation of the anterior hypothalamus (preoptic area) calls forth a decrease in the rate and depth of respiration which is frequently associated with a fall of the blood pressure (190, 258). Hess (148) regards the increased respiration as a part of the ergotropic (sympathetic) and the decreased respiration as a part of the endotropic-endophylactic (parasympathetic) integrations which are the specific functions of the posterior and anterior parts of the hypothalamus respectively.

On the basis of these data an investigation was undertaken which, although less complete, roughly parallels our earlier vascular studies. The work may, therefore, be presented in two parts, one concerned with the influence of the hypothalamus on the level of respiratory activity, the other with the role of the hypothalamus in reflexes which either increase or decrease respiration.

NOTE. The basis of this chapter is unpublished work in collaboration with E. S. Redgate.

## *Experimental Investigations*

### A. THE HYPOTHALAMUS AND THE LEVEL OF RESPIRATORY ACTIVITY

The first group of experiments concerns the effect of the functional elimination of the posterior hypothalamus on the level of respiratory activity, as indicated by the pneumogram. In nine cats pentothal was injected bilaterally into the posterior hypothalamus and its effect on respiration, blood pressure, and heart rate was recorded. In seven cats the respiration was markedly decreased upon injection, whereas in two cats no change was recorded. The decrease in respiration was in part due to a diminution of the frequency, in part also to a diminution of the amplitude of respiration, although a diminution of frequency with a (compensatory?) increase in the amplitude was also observed. In three cats in which chloralosane was used for the initial anesthesia the injection of the barbiturate led to a cessation of breathing so that artificial respiration had to be administered. After 15 to 30 minutes, as the action of the intrahypothalamically injected anesthetic began to wear off, spontaneous respiration reappeared. In the other successful experiments mentioned above, the respiration returned to the pre-injection level after a similar interval of time.

In some experiments a simultaneous recording of the blood pressure and heart rate after the injection of pentothal into the posterior hypothalamus showed the typical changes in blood pressure and heart rate described for cats with an artificially maintained, constant respiratory volume (see Chapter 2, Section E). That is, the decrease in respiration was associated with a decrease in the blood pressure and heart rate. In other experiments the blood pressure and heart rate behaved differently, apparently owing to secondary influences resulting from the lessened respiratory volume. Thus Figure 77 shows that as the respiratory rate was markedly slowed, the blood pressure began to rise, and the heart rate was slightly accelerated. These sympathetic vascular effects are indubitably due to an excitation (reflexly and directly) of the sympathetic system by an increasing degree of asphyxia. As the

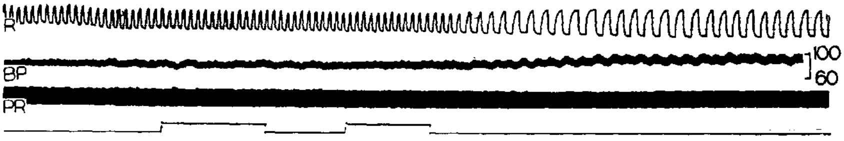

*Figure 77.* The effect of bilateral injection of 1 mg. pentothal into the posterior hypothalamus (indicated by the signal magnet) on respiration (R), blood pressure (BP) and pulse rate (PR). Bar at left upper part of figure = 10 seconds. Note that following the second injection the respiratory rate is greatly reduced while a slight compensatory rise of the blood pressure occurs.

last section of Figure 77 indicates, this homeostatic reaction counteracted the slowing of the respiration induced by the intrahypothalamic injection of pentothal.

In another series of experiments, the posterior hypothalamus was coagulated bilaterally.* In six of nine cats this procedure was accompanied by a distinct decrease in respiratory activity, whereas in three animals the respiratory activity was practically unchanged. The changes in respiratory activity and also the changes in the blood pressure and heart rate were similar to those described in the intrahypothalamic injection experiments.

It may be concluded from these experiments that the posterior hypothalamus furnishes facilitatory impulses to the medullary respiratory center, since the functional elimination of the posterior hypothalamus by drug action or by high frequency coagulation leads to a distinct lessening of the respiration in rate and amplitude.

In a second series of experiments the anterior hypothalamus was coagulated in seven cats. In five cats the respiratory activity was increased either in frequency or in amplitude or in both. In one cat the respiration was unchanged, and in one it was decreased.

## B. RESPIRATORY REFLEXES AND THE POSTERIOR HYPOTHALAMUS

Electrical stimulation of an afferent nerve (sciatic) and asphyxia served to stimulate respiration, whereas the Hering-Breuer reflex served to inhibit it. These stimuli were applied before and after the posterior hypothalamus was partially eliminated either by high-frequency coagulation or by the injection of pentothal into this structure. The results were uniform and, in the injection experiments, reversible.

If the sciatic nerve was stimulated with condenser discharges or square-wave currents of suitable parameters, the frequency of respiration increased. This effect was confined to the period of stimulation when stimuli of moderate intensity were used. Depending on the intensity of the stimulus, this excitatory effect of sciatic nerve stimulation was either greatly reduced or abolished after functional elimination of the posterior hypothalamus.

When the trachea was clamped, asphyxia caused the amplitude of the respiratory movements to increase considerably (Fig. 78*A*). After injection of pentothal into the posterior hypothalamus this effect was greatly reduced (*B*) but restored to a considerable degree about 40 minutes after the injection (*C*). From results such as this, obtained in in numerous tests, it may be concluded that the excitatory effect of

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* The histology will be published in a final paper.

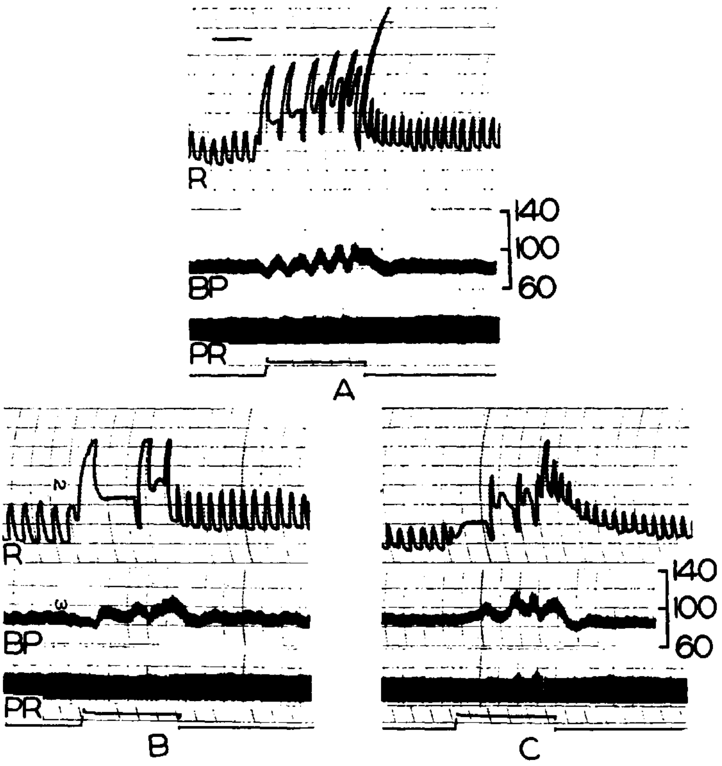

*Figure 78.* The effect of bilateral injection of pentothal in the posterior hypothalamus on the action of 30 seconds asphyxia. Same cat as in Figure 77. Note that the respiratory excitation during asphyxia is greatly lessened after the injection (*B*) and that the effect is reversible (*C*).

*A.* 30 seconds asphyxia at 1:20 P.M. Between *A* and *B*, at 1:35 P.M. intrahypothalamic injection of pentothal. *B* and *C*. 30 seconds asphyxia at 1:51 and 2:16 P.M. respectively.

asphyxia on respiration is greatly reduced by functional elimination of the posterior hypothalamus. The records also show that this result obtains regardless of whether or not the blood pressure response to asphyxia is altered by the intrahypothalamic procedures.

We turn now to the inhibitory respiratory reflexes. The classic Hering-Breuer reflex was employed. At the height of the inspiration 40 cc. of air was injected into the trachea. After a delay of several seconds, a respiratory movement was recorded in the control test (Fig. 79*A*). As soon as two respiratory movements had been recorded, the syringe was removed and the normal intratracheal pressure was restored. This experiment was repeated (Fig. 79*B*) after pentothal had been injected intrahypothalamically. Although the increased pressure

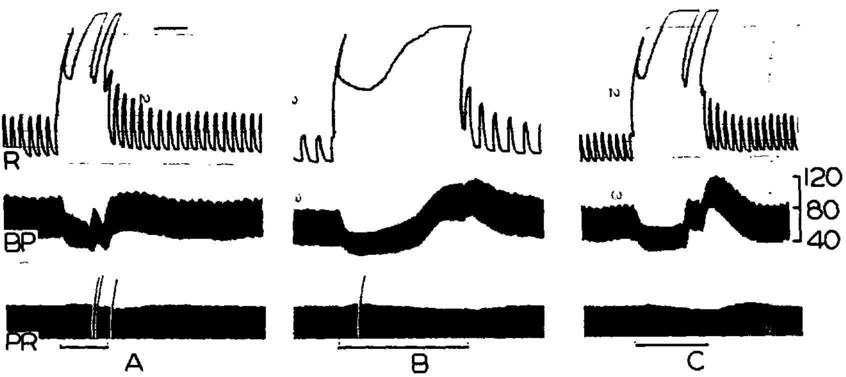

*Figure 79.* The effect of bilateral injection of pentothal in the posterior hypothalamus on the Hering-Breuer reflex. During the time indicated by the horizontal line the lungs were kept inflated by the injection of 40 cc. air. Note that respiratory movements ceased completely after the intrahypothalamic injection of pentothal (*B*) and that the effect was reversible.

At the beginning, at the horizontal line, 40 cc. of air was injected intratracheally. Between *A* and *B* pentothal (1 mg.) was injected intrahypothalamically. *C*. Approximately 30 minutes after the injection.

was maintained for approximately twice as long as in the control tests, respiratory movements did not occur. After the effect of pentothal had worn off, a reactivity similar to that recorded in test *A* was reestablished (Fig. 79*C*). Experiments of this type suggest that functional elimination of the posterior hypothalamus greatly increases the inhibition of inspiration which results from an inflation of the lungs.

## C. EVALUATION

Two important facts emerge from the experiments reported in this chapter: (a) that the level of respiratory activity is decreased after lesions of the posterior hypothalamus, and increased after lesions of the anterior hypothalamus; (b) that stimuli which increase respiration become less effective, and those which diminish respiration reflexly become more effective, after functional elimination of the posterior hypothalamus.

Apparently there is a close parallelism between the influence of the hypothalamus on circulation (indicated by the blood pressure and heart rate) and on respiration. The posterior hypothalamus furnishes excitatory impulses to the sympathetic medullary centers and also to the respiratory center. On the other hand, judged by the alteration in the level of respiration, blood pressure, and heart rate, the anterior hypothalamus appears to inhibit circulation and respiration.

It was shown earlier that the principle of reciprocal innervation regulates the relative activity of the anterior and the posterior hypothalamus. Thus a reduction in excitability of the posterior hypothalamus not only reduces sympathetic discharges but releases parasympathetic action. That similar specific relations between the hypothalamus and the medullary (and pontine) respiratory centers exist is conceivable. The problem of how lesions at the hypothalamic level alter the activity of the inspiratory and expiratory centers in the medulla oblongata, however, lies beyond the scope of our investigation.

Although the effect of anterior hypothalamic lesions on excitatory and inhibitory reflexes has not yet been investigated adequately, the striking changes produced in these reflexes through posterior hypothalamic lesions permits one to recognize an important principle. Respiratory reflexes, such as the Hering-Breuer reflex inhibiting respiration via the vagus, are usually considered to be medullary reflexes.* The excitatory action on respiration of stimulating the sciatic nerve and of asphyxia—the latter involving in part the chemoreceptors of the sino-aortic area, in part the central nervous system directly—is likewise said to be mediated by the medulla oblongata. The persistence of these reflexes in deep anesthesia and also in the decerebrate preparation proves the correctness of this statement. Nevertheless, the fact that a lesion in the posterior hypothalamus or temporary reductions in its excitability reduce the magnitude of these reflexes indicates that the *reflex threshold* and the degree of response to suprathreshold stimuli are determined, other conditions being equal, by the intensity of the posterior hypothalamic discharge. This discharge determines also the resting level of respiratory activity. It should be emphasized that this discharge is a *physiological function* of the hypothalamus and not only, as Pitts (250) assumes it is, the result of emotional stress. Since the heart rate and level of the blood pressure and the excitatory reflexes which increase these vascular functions are also lessened by lesions of the posterior hypothalamus, whereas inhibitory (vagal) reflexes are intensified, it may be said that the action of the posterior hypothalamus is similar for the respiratory and circulatory functions studied thus far.

Although respiratory and vascular reactions have been shown to be intimately related to one another in various forms of physiological activity and under conditions of direct and reflex stimulation of the central nervous system at various levels, the changes in the level of respiration and in respiratory responsiveness associated with alterations in hypothalamic excitability are independent of the changes in vascular activity and responsiveness. How the blood pressure and heart rate are altered in a specific manner after anterior and posterior hypothalamic lesions (or injections of pentothal into these structures) in curarized animals with constant respiration has been described in Chapter 2 (Section E). That the changes in respiratory reactivity following these intrahypothalamic procedures are independent of associated changes in vascular reactions is evident from the experiments on asphyxia. Thus, depending apparently on the degree of anesthesia and the duration of asphyxia, the pressor response to asphyxia was retained in some experiments, whereas in others it was converted into a depressor response after the excitability of the posterior hypothalamus had been reduced experimentally. In both instances, however, the respiratory responsiveness was lessened.

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* See, for instance, item 250.

The fact that the level of respiratory activity and the sensitivity of common respiratory reflexes are determined in part by the hypothalamus makes easily understandable why emotional disturbances are frequently associated with respiratory symptoms. It also accounts for the lessened respiratory responses of psychotic patients in conditions of stress (72). The experimental work discussed in this chapter suggests that respiratory tests may be useful indicators of alterations in hypothalamic reactivity in man. Such tests may be expected to show a parallelism between the degree of sympathetic responsiveness (as indicated, for instance, by the mecholyl test) and respiratory reactivity.

## CHAPTER 7

# THE HYPOTHALAMIC-CORTICAL DISCHARGE AND ITS RELATION TO THE STATE OF THE HYPOTHALAMIC BALANCE

IF IT is correct, as Sherrington (280) argued convincingly, that to investigate the integrative action is one of the chief tasks of a physiology of the central nervous system, it follows that no physiological investigation of central nervous functions should be limited by artificial anatomical boundaries. Particularly is this true of the study of autonomic functions. An understanding of the role of the autonomic nervous system in the organism is unthinkable without considering its intimate relation to the endocrine system (87, 94, 141). But it is necessary to go even further. Langley (208) thought of the autonomic nervous system as an efferent system only. From this point of view the purpose of an autonomic physiology would be to clarify the function of the peripheral autonomic nerves and their connections and relations to the autonomic central structures located within the cerebrospinal system. Or, to express this problem in physiological rather than anatomical terms, it would appear to be the task of the physiology of the autonomic nervous system to analyze the nature and significance of the "downward" discharge (Cannon) which under a variety of physiological conditions may originate in the autonomic system or may be elicited in it through afferent somatic or visceral impulses. The investigations discussed so far in this book fall within the framework of this classic autonomic physiology. But Cannon already realized that the functional effect of central autonomic processes was not confined to the downward discharge. He postulated, in addition, an "upward" discharge which, originating in the diencephalon, would influence the cerebral cortex and thereby account, for instance, for the qualitative changes in sensations and perceptions which occur in emotional excitement.

An outline of the work through which the nature of the upward discharge has been established will be given in the following pages. Furthermore, it will be shown that this hypothalamic-cortical discharge, which is basic for the maintenance of those cerebral processes on which conscious activity depends, is greatly altered when the state of the autonomic balance is changed in the hypothalamus. This finding enlarges considerably the scope and the significance of our investigations. It suggests that disturbances of autonomic functions at the hypothalamic level may fundamentally influence cortical processes and thereby behavior. As a corollary it seems to follow that changes in behavior resulting from an alteration in hypothalamic functions and consequently from a change in the hypothalamic-cortical discharge may occur when an attempt is made to redress the disturbed hypothalamic functions.

Finally, the well-known fact that the cerebral cortex influences diencephalic functions suggested an investigation of the effect of cortical stimuli on autonomic functions in conditions of hypothalamic autonomic imbalance. The results and implications of these studies for the hypothalamic-cortical discharge will be discussed.

## A. PROOF OF THE EXISTENCE OF THE HYPOTHALAMIC-CORTICAL DISCHARGE

A hypothalamic-cortical discharge was shown to exist in experiments involving stimulation and functional elimination of the hypothalamus. These studies were guided by the fact that Cannon (37) had postulated an upward discharge in emotional excitement and Bard (9) had shown that the diencephalic area indispensable for the display of the autonomic discharge accompanying emotion is located in the posterior hypothalamus. Electrical stimulation of this structure led to a diffuse excitation of the whole cerebral cortex (242, 243). This excitation was indicated in the anesthetized animal by the disappearance of the grouped ("Dial") potentials and their replacement by smaller and more frequent potentials. In addition to this asynchrony of the cortical potentials, it was noted that strong stimuli increased the amplitude of the potentials, a result suggesting the recruitment of previously inactive neurons. Finally, if strychnine spikes were produced at one or more sites of the cerebral grey matter through local application of this drug, hypothalamic stimulation led to an increased frequency of these convulsive discharges. These phenomena of cortical excitation occurred, as was stated earlier, in the cortex as a whole, but they were stronger in the hemisphere ipsilateral to the site at which the hypothalamus was stimulated.

The generalized excitation of the cerebral cortex and the characteristic downward discharge activating the sympathetic nervous system that result from electrical stimulation of the posterior hypothalamus may be considered to be a physiological model for the processes that go on when the posterior hypothalamus is hyperactive, as during emotional excitement, but this "model" needs to be supported by further experimental data showing that such a hypothalamic-cortical discharge occurs when the hypothalamus is activated by more physiological means. For this purpose the action of various reflexes on the hypothalamic-cortical system was studied.

Such data are provided through a study of the action of nociceptive impulses on the hypothalamus and the cortex. When in our experiments the sciatic or another afferent somatic nerve was stimulated electrically, the posterior hypothalamus was found to be excited and this excitation was accompanied by a generalized excitation of the cerebral cortex (101). Later (93), an even more physiological method to evoke nociceptive impulses (and pain sensation) was used—the immersion of the foot or the tail of the cat in hot water. Here again the stimulus caused an excitation of the hypothalamus and cortex which paralleled the degree of nociceptive stimulation. If the blood pressure, the nictitating membranes, the pulse rate, and the width of the pupils were recorded at the same time, the hypothalamic upward discharge was found to be associated with a downward discharge leading to sympathetic effects on these indicators. In "light" animals, vocalization and movements occurred also.

It may be concluded from these experiments that nociceptive impulses induce a generalized hypothalamic-cortical discharge. The absence of this discharge and of the objective signs commonly associated with the appearance of pain in deep narcosis on the one hand, and the close relation existing between pain and emotion on the other, may be considered to be an indication of the physiological role which the hypothalamic-cortical discharge plays in the genesis of pain.

It is well known that the inhalation of carbon dioxide causes reflexly (via the chemoreceptors of the sino-aortic area) and directly an increased downward discharge from the sympathetic autonomic centers in the medulla oblongata and the hypothalamus. This observation suggested that the hypothalamic-cortical discharge would also be augmented if it is true that an increased excitability of the hypothalamus would lead to an increased "downward" *and* "upward" discharge. Figure 80 illustrates a pertinent experiment (93, 95). The hypothalamic potentials in the control periods preceding and following the administration of carbon dioxide were large and in part grouped, although the grouping was not as sharply delimited as in the "Dial" potentials recorded from cortical sites. Two other cortical areas were strychninized. Strychnine spikes of irregular amplitude were recorded with the third channel while the potentials of the last channel were a mixture of

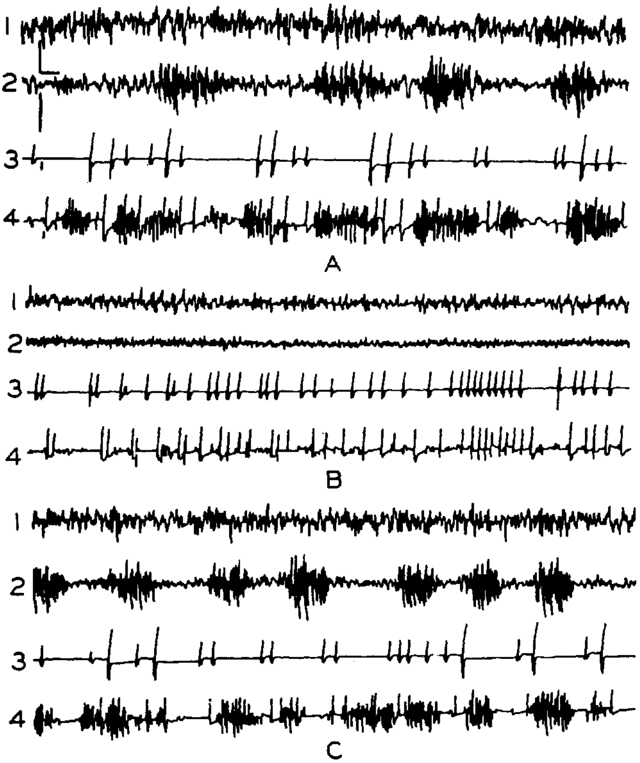

*Figure 80.* The effect of 10 per cent $CO_2$ on hypothalamic and cortical potentials in a cat anesthetized with pentothal. Note that $CO_2$ causes excitation in the hypothalamus and cortex characterized by the appearance of fast potentials of low amplitude in the normal cortex and hypothalamus and by increased strychnine spikes in the strychninized cortex, Gellhorn (93).

*1*. Right hypothalamus. *2*. Left motor cortex. *3*. Left occipital cortex, strychninized. *4*. Right occipital cortex, strychninized. *A*. Control in air. *B*. After 2 minutes in 10 per cent $CO_2$. *C*. 3½ minutes after air had again been administered. Calibration: 300 microvolts and 1 second.

grouped and spike potentials.* Cortical and hypothalamic potentials underwent similar changes during hypercapnia: the grouped potentials disappeared (channels *1*, *2*, *4*). The small, frequent potentials which took their place signify an increased degree of asynchrony. The excitatory character of these changes is further indicated by the marked increase in the frequency of the spike potentials (channel *3*).

If the animals were "light" or the concentration of carbon dioxide was slightly stronger, evidence of even higher degrees of hypothalamic and cortical excitation was found: the hypothalamic and cortical potentials increased in frequency and also in amplitude (recruitment). Moreover, it was found that in cats injected with subconvulsive doses of picrotoxin, the stimulation of the hypothalamus (103), afferent nerves (sciatic), or sense organs (through optic or acoustic stimuli) likewise induced generalized convulsive discharges in the cerebral grey matter. These discharges were associated with and paralleled by discharges in the posterior hypothalamus (102). According to these investigations, then, *the hypothalamic-cortical discharge may be elicited by direct and reflex activation of the posterior hypothalamus. This discharge appeared in the normal animal in the form of a generalized excitation of the cerebral cortex, whereas in animals in a subconvulsive state a spread of the convulsive discharges occurred over the whole cerebral cortex.*

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* This is due to the fact that the response of the cortex to strychnine was less at the site recorded in channel *4* than that seen in channel *3*.

Further experiments showed that the hypothalamus released from the control of the cerebral cortex (in anoxia or asphyxia) gives rise to a characteristic hypothalamic-cortical discharge (104).

## B. THE PHYSIOLOGICAL SIGNIFICANCE OF THE HYPOTHALAMIC-CORTICAL DISCHARGE

The experiments described in the preceding pages show that the cortical discharge initiated by an excitation of the posterior hypothalamus is diffuse in character. This diffuseness distinguishes it from the afferent discharges originating in specific sense organs, such as the eye or the ear, which cause an excitation that is confined to a specific cortical projection area. The fact that the hypothalamic discharge affects the cerebral cortex as a whole (and apparently also the cortex of the cerebellum) suggests that these impulses provide the cortical neurons with something essential for their activity regardless of the nature of the specific function which any particular area of the cortex may exert.

There is a clue to the significance of these diffuse changes for the cortical activity in an electroencephalographic observation of Berger (19). He found that states of increased attention and mental activity are associated with a generalized cortical excitation which leads to the disappearance of the alpha potentials and their replacement by the more frequent and smaller beta potentials. Similar signs of a generalized state of increased asynchrony of cortical discharges were observed in unanesthetized animals on arousal (265).

With these investigations as a background, we determined the correlation between cortical activity, hypothalamic excitation, and the arousal reaction under the influence of various afferent stimuli (21).

Experiments performed on cats and monkeys in different states of anesthesia showed that in very "light" animals arousal reactions, characterized by pupillary dilatation and movements of the eyes and the limbs, occurred in response to nociceptive, proprioceptive, and acoustic stimuli (listed in the decreasing order of effectiveness). Here again arousal was accompanied by a generalized excitation of the cortex, indicated by the disappearance of the grouped potentials and a state of asynchrony of cortical neuronal discharges. There was a high correlation between the diffuse cortical excitation and an excitation of the hypothalamus, as indicated by the following data. Of a total of 41 nociceptive stimuli which induced a generalized reaction of the cerebral cortex, 39 (95 per cent) showed excitation in the hypothalamus; the corresponding figures for proprioceptive stimuli were 64, with 53 (83 per cent) hypothalamic reactions. Auditory stimuli caused generalized reactions only infrequently.

The correlation existing between the intensity of the sensory effect on the cortex and the frequency and often also the degree of hypothalamic activation is obvious. In addition, in most instances specific cortical excitation was not accompanied by activation of any part of the hypothalamus. All 24 optic experiments induced specific effects on the visual cortex and no excitation of the hypothalamus. Of 69 acoustic experiments, only 1 showed hypothalamic excitation associated with specific cortical reactions.

To show this important parallelism between the type of cortical excitation and the occurrence of hypothalamic excitation, arousal reactions were attempted in the same animal with different types of stimuli, as illustrated in Figure 81. Section *A* of the figure shows that there was a *partially generalized* cortical reaction with activation of the lateral mammillary nucleus in response to proprioceptive stimulation.* Section *B* illustrates the *generalized* cortical excitation of all cortical areas and activation of the lateral mammillary nucleus in response to pain stimulation. In sharp contrast to these reactions is the specific response to acoustic stimulation illustrated in Section *C*: a "following" of the sound is seen in the auditory area, while there was no excitation in the sensorimotor and optic areas nor any activation of the lateral mammillary nucleus. In this experiment signs of arousal were present on proprioceptive and nociceptive stimulation, but absent on acoustic stimulation.

From this work it may be concluded that the state of awareness is linked with the activation of the hypothalamic-cortical system. De-

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* There was not a clear excitation of the auditory cortex.

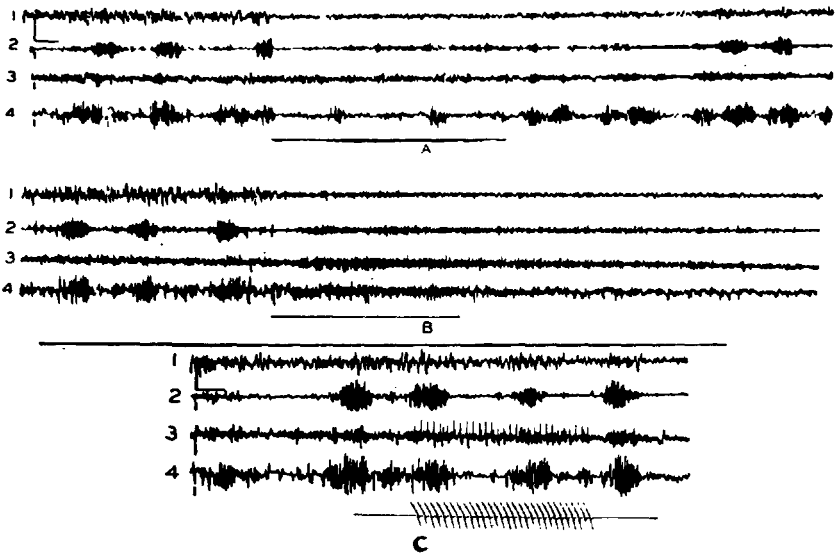

*Figure 81.* The effect of various afferent stimuli on cortex and hypothalamus. *A*. Partially generalized cortical response with activation of posterior hypothalamus in response to proprioceptive stimulation. Excitation in lateral mammillary nucleus, sensorimotor and visual areas, and no excitation in auditory area. *B*. Generalized cortical response with activation of posterior hypothalamus in response to nociceptive stimulation. *C*. Specific response of auditory cortex to acoustic stimuli. No excitation in hypothalamus and other cortical areas, Bernhaut, Gellhorn, and Rasmussen (21).

*1*. Left mammillary nucleus. *2*. Left sensorimotor area. *3*. Left auditory cortex. *4*. Left visual cortex. Calibration: 100 microvolts and 1 second. Stimulation indicated by horizontal bar.

pending on the state of anesthesia, the modality of the sensory stimulation involved, and the intensity and duration of the stimulus, the symptoms of awareness and their intensity and duration varied considerably, as did the degree, the duration, and the areal extent of the cortical excitation.

Since the diffuse cortical excitation which seems to be associated with the state of awareness showed a high degree of correlation with hypothalamic excitation, it was thought that it would be possible to show the specific role of the hypothalamus in these processes by investigating the influence of hypothalamic lesions. Systematic studies (201) showed that unilateral lesions in the posterior hypothalamus greatly reduced or abolished the effect of nociceptive stimulation (and also the diffuse excitatory effect of 10 per cent carbon dioxide) on the ipsilateral cortex. After another lesion in the homologous area of the other side was added, a further reduction or a complete disappearance of the generalized cortical excitation occurred. It is worthy of note that the lesions had this action only if they involved the posterior but not the anterior hypothalamus.*

The extensive investigations of Magoun and his collaborators (75, 213, 214, 221–223) established the anatomical basis of this diffuse excitatory effect that is the basis of general awareness. Their most important experiments concern cats and monkeys with chronic bilateral lesions in the brain stem; they studied the effect of these lesions on the behavior and the electrocorticogram of these animals and came to the following conclusions. Lesions in the lateral part of the mesencephalon which eliminate the medial and lateral lemnisci and spinothalamic tracts do not lead to significant changes in behavior and posture. Such animals show normal sleep cycles and are aroused by appropriate stimuli. These states are accompanied by typical changes in the EEG, as in normal animals. However, lesions involving the midbrain tegmentum or extensive destruction of the hypothalamus are associated with somnolence or coma. The animals can be aroused from this state, but stimuli of greater intensity are required than in normal sleeping cats, and the effect is frequently confined to the period of stimulation.

On the basis of experiments with stimulation, it may be said that excitatory processes are carried to the cerebral cortex from peripheral receptors via two sharply differentiated systems. The first is that of the long afferent fiber tracts, such as the medial lemniscus and the spinothalamic system, which carry impulses from exteroceptors and interoceptors to specific projection areas. The second, which accounts for the diffuse excitatory effects, may be called the facilitatory system of Magoun, which originates in the tegmentum of the midbrain and

* There is an interesting discrepancy between the experiments of Bernhaut *et al.* (21) showing that the diffuse cortical excitation resulting from afferent stimuli is accompanied by an excitation of the anterior, intermediate, and posterior parts of the hypothalamus, and the lesion experiments of Koella and Gellhorn suggesting that the posterior hypothalamus has a specific role. It seems that the specific structure necessary for the diffuse cortical effect can be determined with greater certainty on the basis of lesions than through experiments involving excitation. Nociceptive stimuli, for instance, lead to an excitation of the posterior hypothalamus. From there the excitation may spread to other parts of the hypothalamus, although these parts do not seem to play an essential role in the transmission of impulses from the hypothalamus to the cortex. The injection of barbiturates or the production of well-circumscribed lesions caused specific functional differences when these procedures were applied to the anterior and to the posterior hypothalamus. However, we have not yet succeeded, by stimulating the anterior hypothalamus, in producing regular and exclusively parasympathetic effects (and a state of parasympathetic tuning), whereas a specific sympathetic effect was easily obtained by stimulation of the posterior hypothalamus. One of the chief reasons for this result is, of course, the spread of excitation within the hypothalamus (and the dominance of the sympathetic division), whereas the barbiturate and lesion experiments were not vitiated by a spread beyond the experimentally afflicted area.

activates the posterior hypothalamus and hence both cortical hemispheres through a diffuse thalamic system involving chiefly the ventromedial group of thalamic nuclei.*

The observations of Lindsley *et al.* (213, 214) that coma results from sectioning the reticular substance in the brain stem, our findings indicating that arousal leads to a diffuse activation of the cortex and is associated with an excitation of the posterior hypothalamus, Ranson's experiments (255, 256) showing that bilateral lesions of the posterior hypothalamus lead to somnolence, and Hess's demonstration (153) that stimulation of this area causes psychomotor excitation, give a firm basis for the statement that awareness in its different degrees—varying from coma, sleep, and somnolence to wakefulness, increased attention, and psychomotor excitation—is associated with the activation of a diffuse afferent system. In this treatise it is called the hypothalamic-cortical system in order to emphasize the fact that the state of the hypothalamus has a profound influence on it.

The fact that two afferent excitatory systems exist which affect the cerebral cortex raises the question whether these two systems interact with each other and, if so, what the effect and the significance of such interaction are. For this purpose the interaction between a specific afferent system activated by acoustic or optic stimuli and the diffuse system excited either by nociceptive stimulation or by electrical stimulation of the posterior hypothalamus (122, 123) was studied through the recording of the electrocorticogram.

Figure 82 reproduces a record in which potentials were taken from three different sites in the ectosylvian gyrus, but only the site recorded from site 1 responded distinctly to the acoustic stimulus. When, however, this stimulus was combined with a nociceptive stimulus, all three sites responded vigorously, although the nociceptive stimulus was so weak that no change of the cortical potentials was seen when it was given by itself. The intensification of the acoustic (and, similarly, of the optic response) appeared not only in the increased size of the cortical area responsive to acoustic stimuli but also in the intensification of the individual cortical auditory or visual action potential. The potentials showed a greater amplitude or a tendency toward multiple responses not seen under control conditions.

The interaction between the two afferent systems became most distinct when local strychninization of a site within the specific cortical projection area was resorted to. Mild nociceptive stimuli, which

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* For further details see item 94 and the symposium on "Brain Mechanism and Consciousness" (26).

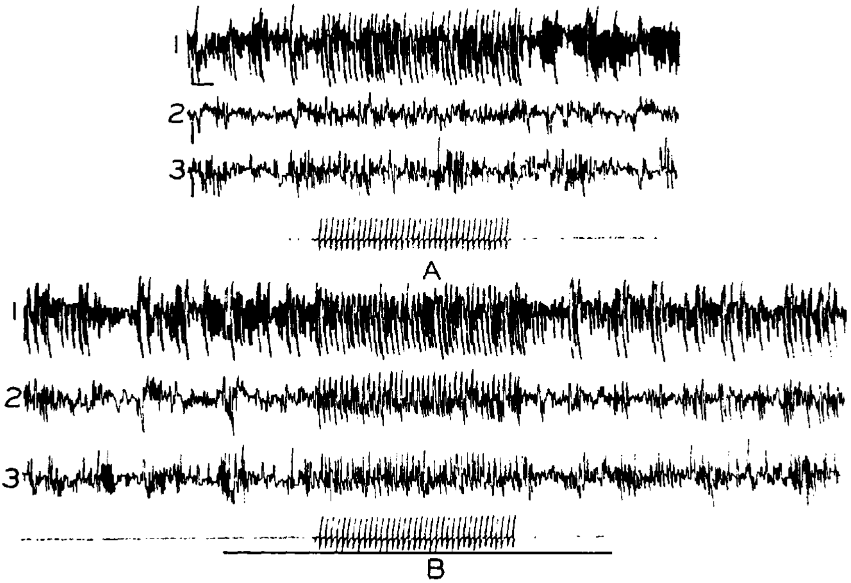

*Figure 82.* The effect of nociception on the responsiveness of the auditory cortex to acoustic stimuli. Note that during nociceptive stimulation, the area and intensity of the cortical auditory response are greatly increased, Gellhorn, Koella, and Ballin (122).

Site *1* (strychninized) and *2* in left, and site *3* in right auditory cortex. The *fourth line* in *A* indicates the acoustic stimuli; the horizontal line in *B* the nociceptive stimulus (immersion of the right hindleg into water of 55° C.). Calibration: 300 microvolts and 1 second.

did not alter the convulsive potentials, greatly increased the responsiveness of the auditory and visual cortex. Convulsive spikes appeared at each site in synchrony with the specific afferent stimuli, even from those sites of the cortex which did not respond to the visual or acoustic stimuli in the absence of nociception.

When the posterior hypothalamus was directly stimulated (rather than by a nociceptive stimulus), the auditory and visual action potentials were augmented in a similar manner (123). That the results are due to a neurogenic interaction (whether at the cortical, thalamic, or both levels has not yet been determined) and not to a rise of the blood pressure is clear for the following reasons: (a) Striking examples of summation occur although the blood pressure remains unchanged.* (b) In experiments in which the blood pressure rises, the increased cortical responsiveness may appear a considerable time after the maximum of the pressor effect, and it may continue while the pressure falls to or slightly below the control level. (c) Slight changes of intensity or frequency of sensory (acoustic or optic) stimulation may abolish the summation, although the pressor effect remains unaltered.

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* It is notable that increasing intensity of hypothalamic stimulation may increase the summation phenomenon and its duration (shortening the summation time and increasing the after effect) in the absence of a pressor effect.

It is interesting to note that the increased cortical excitation which results from the interaction between sensory impulses and hypothalamic stimuli is not restricted to the specific projection area. Although summation processes are most pronounced in the auditory projection area, if acoustic and hypothalamic stimuli are applied at the same time, this combination of stimuli may exert a greater excitatory effect on the visual projection area than either form of stimulation when presented alone.

Since the stimulation of the posterior hypothalamus exerts an excitatory effect on all cortical sites, it was thought that the afferent impulses thus elicited might also increase the centrifugal impulses originating in the motor cortex. Subthreshold stimulation of the posterior hypothalamus was indeed found substantially to augment the effect of stimulation of the motor cortex. Murphy and Gellhorn (242), who made this observation in 1945, were aware of the fact that such interaction may take place at the spinal and the cortical level. They suggested on the basis of their observations that under their experimental conditions the interaction takes place, at least in part, at the cortical level. Rhines and Magoun (266), who confirmed this interaction, noted that such facilitatory effects persisted when the hypothalamic stimulus was combined with an excitation of the pyramidal tracts instead of that of the motor cortex. While this experiment (in which the motor cortex had been removed) proves that the interaction takes place also at the spinal level, it does not eliminate the possibility that a similar (and perhaps even more important) interaction may occur at the cortical level if the brain is intact.

Since certain clinical observations, such as the production of ejaculatory speech in cases of motor aphasia under conditions of emotional stress, suggest strongly a facilitation of the Broca area through afferent impulses, it appears likely that a similar facilitation of the motor area may be induced by afferent impulses from the posterior hypothalamus. To clarify this question, single action potentials from the pyramidal tracts at the medullary level were recorded before and after stimulation of the posterior hypothalamus or before and after nociceptive stimulation in completely curarized cats.* The results were similar in both sets of experiments. As Figure 83 shows, the

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* Unpublished experiments of W. P. Koella and H. M. Ballin.

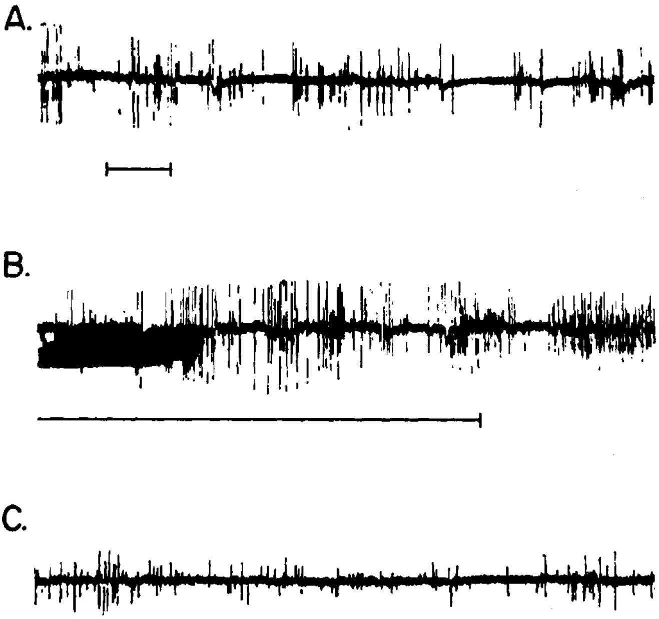

*Figure 83.* The effect of hypothalamic stimulation on action potentials of the pyramidal tracts in the medulla oblongata. Note that during and after hypothalamic stimulation, the pyramidal discharges are greatly increased.

*A.* Before stimulation. *B.* Hypothalamic stimulation, 6 v., 60 pps, 0.1 ms., 15 sec. The bar indicates the end of the stimulation. *C.* One minute after *B.* The time bar equals 0.2 second.

hypothalamic stimulus may lead to a considerable increase in the frequency of the rate of discharge of individual neurons during hypothalamic stimulation and also for some time afterwards. This experiment proves that hypothalamic impulses may induce facilitatory effects also on the motor cortex.*

Since it was noticed in the previously reported studies dealing with the interaction of the specific and diffuse afferent systems that the resulting summation, although most distinct in specific projection areas, is not confined to them, it may be said that *sensory and motor cortical areas and also the "silent" parts of the cortical gray matter are quantitatively altered in their degree of activity and in their responsiveness to specific afferent stimuli by impulses originating in the posterior hypothalamus as the result of direct or reflex activation.*

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* It was also found, as in Arduini's work (7), that sometimes the hypothalamic stimulation reduced the frequency of pyramidal discharges. It remains to be studied what factors (anesthesia?) are responsible for the different types of interaction existing between afferent hypothalamic-cortical impulses and the neurons of the motor area which lead to significant changes in the centrifugal impulses of the pyramidal tracts.

## C. THE DEPENDENCE OF THE HYPOTHALAMIC-CORTICAL DISCHARGE ON THE EXCITABILITY OF THE HYPOTHALAMUS

We have considered certain characteristics of the hypothalamic-cortical discharge and the importance of the integrity of the posterior hypothalamus for the diffuse activation of the cerebral grey matter. We turn now to the role of the functional state of the hypothalamus, and shall discuss first the role of its state of excitability and later (Section D) the influence of alterations in the hypothalamic autonomic balance.

It is easy to show in cats and monkeys that progressive barbiturate anesthesia first diminishes and then eliminates the diffuse excitation of the cerebral cortex in response to proprioceptive and nociceptive stimuli, an excitation dependent on the excitation of the hypothalamus. The parallelism between the hypothalamic excitation and the diffuse excitation of the cortex under the influence of increasing degrees of

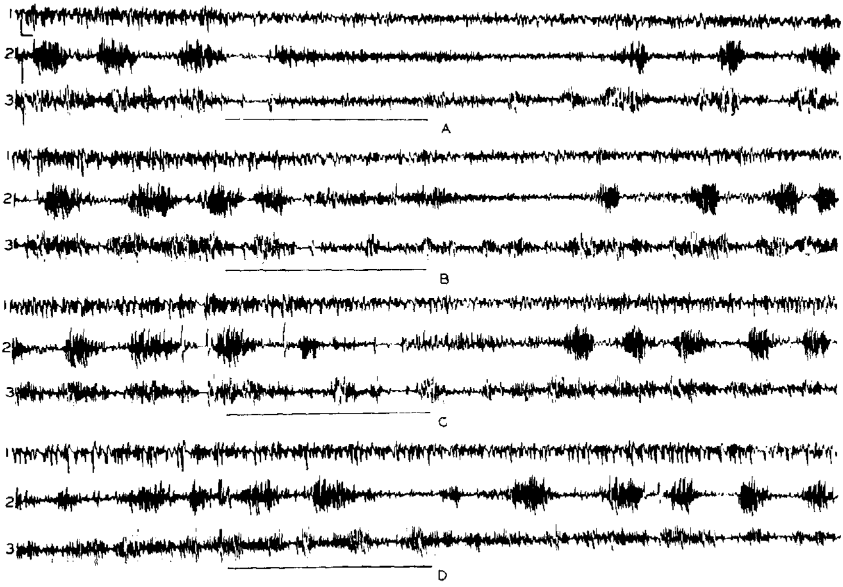

*Figure 84.* The effect of barbiturate anesthesia on the nociceptive response of the cortex and hypothalamus. Note that these responses decrease with increasing barbiturate anesthesia, Gellhorn (96).

5 mg/Kg pentothal was injected i.v. 2½ hours before *A* was recorded. *B.* 4½ minutes later after further injection of 1 mg/Kg pentothal i.v. *C.* 4½ minutes after *B* and after further intravenous injection of 3 mg/Kg pentothal. *D.* 30 minutes after *C* and after further administration of pentothal (5 mg/Kg i.v.). *1.* Right hypothalamus. *2.* Left motor cortex. *3.* Sensory cortex (gyrus suprasylvius). Calibration: 300 millivolts and 1 second. The horizontal line indicates nociceptive stimulation (immersion of right hindleg in water of 60° C. for 20 seconds).

pentothal anesthesia is illustrated in Figure 84. Part *A* illustrates the action of a mild nociceptive stimulus under control conditions, in which the pentothal anesthesia was very light, whereas parts *B, C,* and *D* represent progressive stages of anesthesia induced by the intravenous injection of 1, 3, and 5 mg. of pentothal respectively. A progressive reduction in the effectiveness of nociception on hypothalamic and cortical potentials is seen. However, even in the last stage either optic or acoustic stimulation elicited distinct effects on the action potentials of the specific cortical projection areas.

Similar investigations have been reported by other authors (6, 76). The arousal reaction resulting from the stimulation of the reticular formation of the brain stem was found to be blocked by nembutal and ether, although the reactivity of the cortical projection areas to their specific afferent systems was retained.

These experiments show that the hypothalamic-cortical system (activated from the hypothalamus or from the reticular substance) and the specific afferent systems, both of which act on the cortex, respond differently to changes in the internal environment, so that one system may be put out of function whereas the other system continues to function normally or even to a higher degree. This functional differentiation between the two systems can be accomplished also by carbon dioxide (93) and by marked alterations in the temperature of the body (199). If carbon dioxide is used in concentrations of 10 per cent, it exerts a profound effect on the hypothalamic-cortical system. Its responsiveness to stimuli such as proprioception and nociception is greatly increased. Thus a mild nociceptive stimulus which had only a distinct effect on the motor cortex but exerted little or no action on the normal and convulsive potentials recorded from other cortical areas and from the hypothalamus became highly effective during the administration of carbon dioxide (Figure 85). Asynchrony and neuronal recruitment appear in hypothalamic and cortical records and persist for a considerable time following the cessation of the stimulus. On the other hand, acoustic and optic responses are decreased under these conditions, as Kornmüller and Noell (204) showed on the rabbit (confirmed in my laboratory on the cat). Here the functional effect of 10 per cent carbon dioxide on the two systems is diametrically opposed.

It should be added that when carbon dioxide is administered in anesthetic concentrations (30 to 35 per cent), the results obtained are like those in barbiturate anesthesia. Proprioceptive or nociceptive stimuli which had a profound excitatory effect on the hypothalamic and cortical potentials under control conditions lost this effect (re-

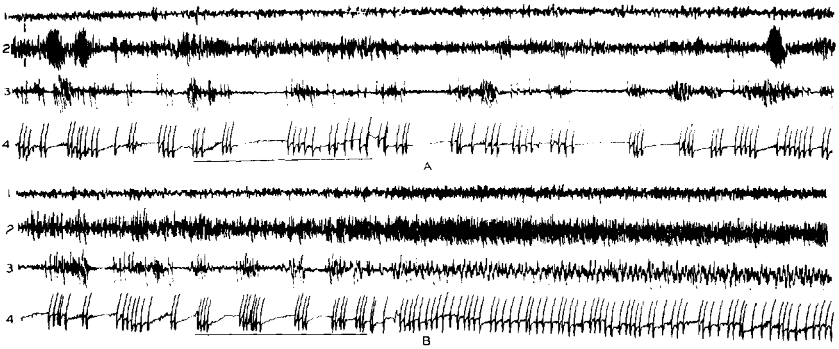

*Figure 85.* The effect of $CO_2$ on the action of nociception on hypothalamic and cortical potentials. Note that the nociceptive stimulus is little effective by itself but causes a great excitation in the hypothalamus and cortex during $CO_2$ inhalation, Gellhorn (93).

Nociceptive stimulus (indicated by horizontal lines): immersion of left hindleg into water of 60° C. for 20 seconds. *A*, before; *B*, 2½ minutes after beginning of 10 per cent $CO_2$. *1.* Right hypothalamus. *2.* Left motor cortex. *3.* Gyrus suprasylvius. *4.* Left occipital cortex. Calibration: 100 microvolts and 1 second.

versibly) under the influence of 35 per cent carbon dioxide. Mild acoustic stimuli, however, still continued to evoke a distinct specific cortical response, although less than in the control test (93, 95).

Furthermore, it was found that through the lowering of the temperature of the body the fundamentally different reactivity of the two afferent systems could be demonstrated. There was a parallelism between the marked decrease of the responsiveness of the hypothalamus to electrical stimuli and the decrease of the responsiveness of the cortex to nociceptive or proprioceptive stimuli; on the other hand, the responsiveness of the auditory area to acoustic stimuli became more distinct and appeared in a larger part of the auditory area (199).

It may be concluded from the experimental work reported in this section that upon the inhalation of 10 per cent carbon dioxide the hypothalamic-cortical discharge is increased, whereas under the influence of 30 per cent carbon dioxide, barbiturates, and a lowered body temperature the hypothalamic-cortical discharge is diminished; only minor (and often even opposite) changes are observed under these conditions in cortical reactions mediated by the specific afferent systems.

The fundamental differences which exist between the hypothalamic-cortical system and the specific afferent systems may be based on the fact that the former involves more synapses than the latter. This seems to be the reason that various anesthetics, high concentrations of carbon dioxide, and low temperature may reversibly eliminate the reticulo-hypothalamic-cortical system at the same time that the functional reactivity of the specific projection systems is retained.

It is important to add that the changes in the hypothalamic-cortical response under various experimental conditions are paralleled by corresponding changes in the responsiveness of the hypothalamus to electrical stimulation, if the indicators of hypothalamic reactivity chosen are the effect on the blood pressure, the pulse rate, and the contraction of the nictitating membrane.

### D. THE DEPENDENCE OF THE HYPOTHALAMIC-CORTICAL DISCHARGE ON THE AUTONOMIC BALANCE OF THE HYPOTHALAMUS

Anesthesia and temperature, on the basis of present knowledge, seem to influence both divisions of the autonomic nervous system in a similar manner. Autonomic imbalance is, on the other hand, characterized by a reciprocal behavior of parasympathetic and sympathetic discharges. It seemed, therefore, desirable to investigate the hypothalamic-cortical discharge in the condition of autonomic imbalance at the hypothalamic level in order to obtain further evidence of the importance of the functional state of each autonomic division for this discharge.

As in the experiments earlier reported (Chapter 2, Section B), an autonomic imbalance was produced by the injection of metrazol, strychnine, or pentothal into the posterior hypothalamus. The reactivity of the hypothalamic-cortical system was tested by nociceptive stimuli. The action of these stimuli was lessened after the intrahypothalamic injection of pentothal. This effect was reversible. Effects were seen with regularity and were partially or completely reversible after about 20 to 30 minutes.

Upon the injection of metrazol into the posterior hypothalamus, the opposite changes occurred. In Figure 86 an experiment is shown in which the excitatory action of a nociceptive stimulus was clearly present at *E*, recorded 25 seconds after the end of the stimulus, whereas at this time in the control test (*B*) the grouped potentials had returned to the prestimulatory level. Moreover, the amplitude of the background potentials was more distinctly increased in the cortical records during the period immediately following the stimulus in the metrazol test *(D)* than in the corresponding control test *(A)*.

From these experiments it may be concluded that the responsiveness of the hypothalamic-cortical system to nociceptive stimulation is altered in opposite manners by the injection of metrazol and pentothal into the posterior hypothalamus. Remembering the fact that nociceptive

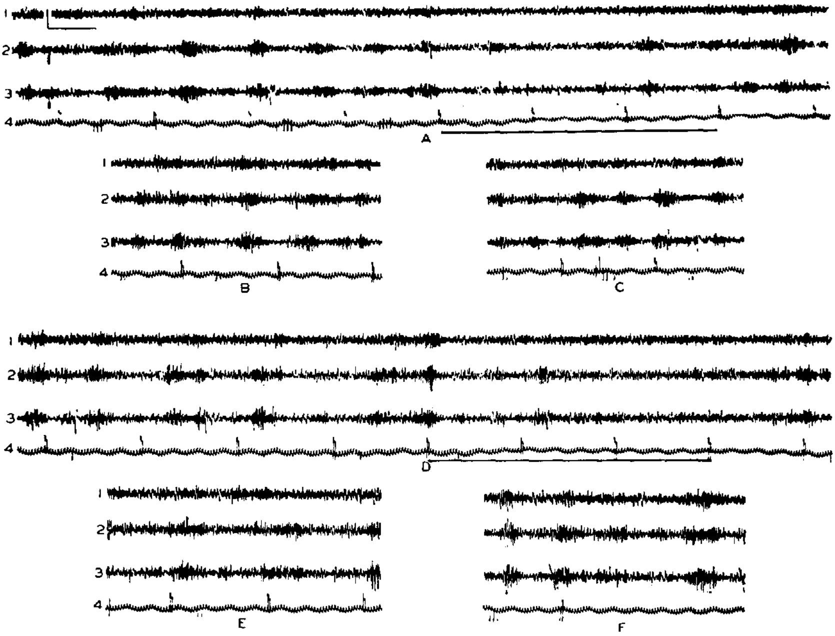

*Figure 86.* The effect of the injection of strychnine into the hypothalamus on the action of nociception. Note that after the injection of strychnine, the nociceptive response is increased.

*A*. Before and during stimulation. (The latter consisted of immersion of the left hind ankle and foot in water of 65° C. for 30 seconds.) *B*. 25 seconds after end of *A*. *C*. 70 seconds after *B*. The records *D*, *E*, *F* were carried out in the same manner after the injection of strychnine. *1*. Right hypothalamus. *2*. Left sigmoid gyrus. *3*. Left parietal cortex. *4*. Blood pressure. Blood pressure level 120 mm. Hg.

stimuli act on the cortex through the reticulo-hypothalamic-thalamic facilitatory system, it may be said that alterations of the autonomic balance at the hypothalamic level alter the hypothalamic-cortical discharge in correspondence with the sympathetic excitability of the posterior hypothalamus.

## E. THE RELATION OF BARORECEPTOR REFLEXES TO THE HYPOTHALAMIC-CORTICAL SYSTEM

It was shown in Chapter 1 (Section B) that changes in the blood pressure through the injection of drugs alter the responsiveness of the hypothalamus. In the experiments reported in Chapter 2 (Section B), it was furthermore demonstrated that changes in the excitability of the hypothalamus produced by various physiological and pharmacological procedures alter the effect of drug-induced changes in the blood pressure. Since these effects are abolished by denervation of the sino-aortic area, the observations suggest a closer relation of the sino-aortic apparatus to the hypothalamus than has heretofore been assumed to exist. In the following experiments an attempt was made to prove the existence of such a relation.

## 1. Hypotensive Drugs and Their Relation to the Hypothalamic-Cortical System

If acetylcholine, mecholyl, or histamine is injected intravenously, while the potentials are recorded from various parts of the cortex in a lightly anesthetized cat, it is found that, as the blood pressure recovers from the hypotension, a state of excitation develops in large sections of the cortex. This state passes gradually over into the resting condition. In animals lightly anesthetized with barbiturates, the grouped potentials characterize the record under control conditions. These potentials are reduced in amplitude or disappear completely as the blood pressure falls; upon its recovery they are replaced by smaller potentials of higher frequency, which represent the electrical equivalent of an excitation process. Gradually this excitation is lessened and the grouped potentials reappear. If strychnine is applied to a cortical area, the excitation appears in the form of an increased frequency of the strychnine spikes, which lends itself to a quantitative evaluation.

In the light of the previously discussed work, this widespread cortical excitation following the drug-induced hypotension suggests that the hypothalamic-cortical system is activated. Experiments* such as that illustrated in Figure 87, in which hypothalamic and cortical potentials are recorded, demonstrate this activation. Because of the greater sensitivity of cortical (and particularly convulsive) potentials to anoxia (115) the spikes disappear from the cortical record for a relatively long time during the hypotensive phase, whereas the hypothalamic potentials are reduced briefly in frequency (see the potentials above the arrow.† Then, in the hypothalamic record, a period showing a marked increase in frequency is followed by one characterized by an increased amplitude. These phenomena indicate and delimit the period of excitation, in which the increased asynchrony of the hypothalamic discharges is believed to account for the increased frequency whereas the increased amplitude suggests the recruitment of neurons not discharging previously. During the latter part of this excitation, a period of increased frequency of spikes appears in the cortex. Toward the end of the record, hypothalamic and cortical activity return to the control level.

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* With the assistance of E. Sigg.

† Note that in some experiments, like that shown in Figure 87, there is a brief initial period of excitation of the cortex shortly after the injection (in the record above the horizontal arrow), which seems to indicate a direct action by acetylcholine on the brain (16, 238). It occurs only when relatively large concentrations of acetylcholine are used.

In this experiment there are several other features worthy of mention. Hypothalamic activity is in general inversely related to cortical. Thus during the fall of the blood pressure (above the horizontal arrow) the cortical spikes become more frequent, while the hypotha-

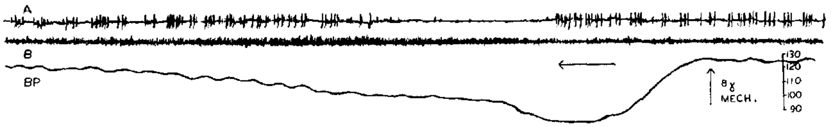

*Figure 87.* The effect of mecholyl on cortical and hypothalamic potentials. Note that as the blood pressure recovers from the mecholyl-induced hypotension the hypothalamic potentials increase in amplitude and frequency and the strychnine spikes become more frequent.

From top to bottom: convulsive potentials from a cortical strychninized area, potentials recorded from the posterior hypothalamus, the blood pressure. Read from right to left. At the vertical arrow 8 gammas of mecholyl is injected i.v.

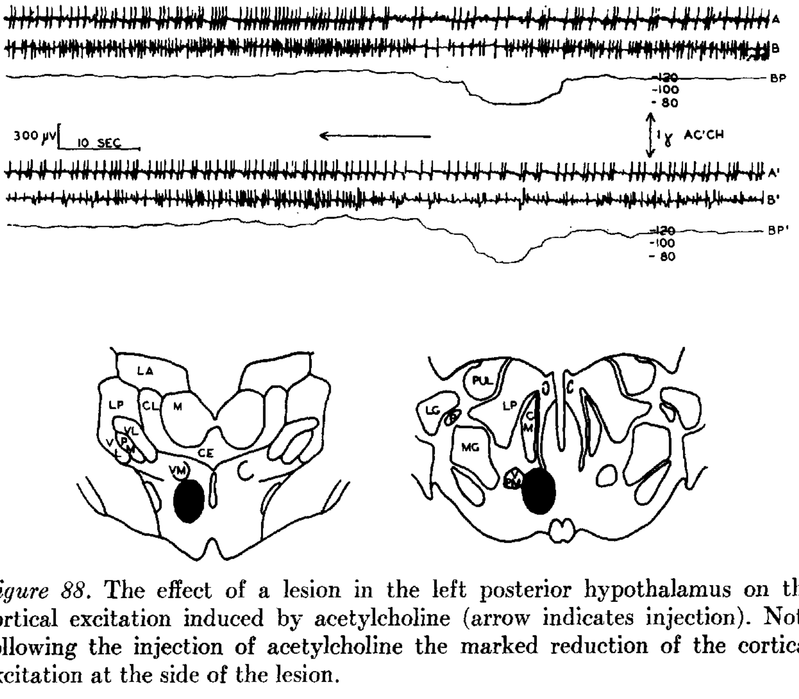

*Figure 88.* The effect of a lesion in the left posterior hypothalamus on the cortical excitation induced by acetylcholine (arrow indicates injection). Note following the injection of acetylcholine the marked reduction of the cortical excitation at the side of the lesion.

*A*. Left cortical site strychninized. *B*. Right cortical site strychninized. *BP* = Blood pressure. The curves on top show the effect of 1 gamma acetylcholine i.v. before, those below after the lesion. Read from right to left.

lamic potentials decline in amplitude. The subsequent disappearance of cortical potentials is, as mentioned above, accompanied by a marked increase in the frequency and number of the discharging hypothalamic neurons (recruitment). This period is followed by one in which the cortical spikes show an increased frequency and during this period the hypothalamic potentials are again less in amplitude.

The fact that the hypothalamic period of excitation begins as the cortical potentials are eliminated suggests that the release of the hypothalamus from cortical inhibition plays a part in the causation of hypothalamic excitation following the injection of hypotensive drugs (104).

Figure 88 illustrates on both cortices the excitatory effect resulting from the injection of 1 gamma of acetylcholine, which is indicated by the greatly increased frequency of the strychnine spikes. In order to investigate the importance of hypothalamic-cortical discharges under these conditions, a lesion was placed in the left posterior hypothalamus and the test was then repeated. Figure 88 shows that the excitatory effect was greatly reduced on the side of the lesion, but retained on the contralateral side.*

The results of nine experiments with unilateral hypothalamic lesions are shown in Figure 89. The excitatory effect of the injection of acetylcholine in the posthypotensive phase was uniformly reduced on the side of the lesion.†

If under these conditions stronger doses of acetylcholine were injected, a distinct excitation could be established also in the cortex on the side of the lesion. These experiments show that the effective lesion reduces but does not block the discharge over the hypothalamic-cortical system.

In three experiments in which, in spite of the application of the high-frequency current to the posterior hypothalamus, no effect was noted, it was later found on histological examination that because of a short in the leads no lesions had been produced. These experiments may be regarded as controls.

The sites of the lesions that were effective and ineffective as far as the acetylcholine-induced diffuse cortical excitation was concerned were studied histologically. It was found that lesions in the posterior hypothalamus and in the ventromedial part of the thalamus dimin-

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* Experiments were also performed after bilateral hypothalamic lesions. The drug-induced excitatory effect was minimal or absent, but such experiments are perhaps less convincing, since the cortical activity and therefore its responsiveness to afferent stimuli are greatly reduced under these conditions (191).

† There is also a greater reduction in the frequency of the spikes during the period of maximal hypotension, as indicated in part *B* of Figure 89.

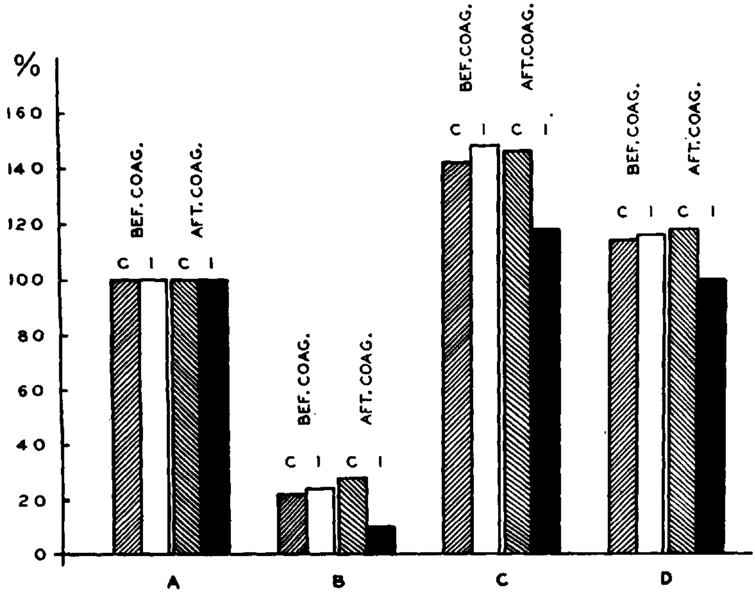

*Figure 89.* Histogram indicating the changes in the frequency of cortical strychnine spikes before and after unilateral lesions in posterior hypothalamus and ventromedial thalamus following the injection of acetylcholine. Note that no significant differences exist in the acetylcholine-induced changes of the spike frequencies between the two sides of the cortex before coagulation. After coagulation, however, the spike frequency is lower ipsilateral to the lesion but as in the control at the opposite side.

Ordinate: Spike frequency in percentage of the control period recorded before the injection of acetylcholine. Abscissa: *A*. Control before injection of the hypotensive drug. *B*. 20–30 seconds after injection of acetylcholine (hypotensive phase). *C*. 40–50 seconds after injection. *D*. 70-80 seconds after injection. The letters *C* and *I* at the tops of the columns indicate, respectively, contralateral and ipsilateral to hypothalamic or thalamic lesion.

ished the acetylcholine-induced excitation of the cortex, whereas lesions restricted to the anterior hypothalamus and the septum pellucidum did not alter the hypothalmic-cortical discharge under these conditions.

Similar experiments were performed with 5 to 20 gammas of histamine (injected intravenously). The excitatory effects on the cerebral cortex obtained with 5 to 10 gammas were regularly abolished by lesions of the posterior hypothalamus, those produced with larger doses (20 gammas) were diminished. The experiments show that hypotensive drugs call forth excitatory effects on the hypothalamus and the cerebral cortex as a whole, as the blood pressure recovers from the hypotensive phase. The phase of increased discharge seems to coincide with the period in which the responsiveness of the sympathetic system to hypothalamic or reflex stimuli is increased. This result suggests that hypotensive drugs, like several other procedures discussed earlier, elicit an upward and a downward discharge from the hypothalamus.

It was mentioned earlier that the hypothalamic-cortical discharge may, through interaction with impulses activating specific cortical areas, greatly increase these specific excitatory phenomena. Thus a hypothalamic stimulus enhances the responsiveness of the cortical auditory area to acoustic stimuli. This phenomenon has been used with great advantage to demonstrate the hypothalamic-cortical discharge following the injection of acetylcholine. A weak acoustic stimulus that evoked only irregular potentials from the auditory cortex elicited regular responses and larger action potentials during the recovery from acetylcholine-induced hypotension. Here again the period of increased cortical reactivity coincided with the excitation of the posterior hypothalamus.

These observations were supplemented by experiments in which the effect of acetylcholine (injected intravenously) on the electrocorticogram was investigated by means of the frequency analysis of the cortical potentials (244). Lines *1* and *2* of Figure 90 show the electrocorticogram of the motor and auditory cortex, line *3* the blood pressure record, and line *4* the frequency analysis of the motor cortex. The cortical potentials discharging at frequencies ranging from 0.5 to 30 per second are added through an Offner analyzer for each frequency during a period of 10 seconds separated by large vertical deflections ("epoch markers"). The various frequencies are separated into five groups through the downward excursions of the lever, and increase from the left to the right.* In the continuous record of Figure 90 it is seen that before the injection of acetylcholine the highest amplitude of the integrated potentials appears in the third group and that the amplitude falls symmetrically at the lower and higher frequencies. This frequency spectrum remains unchanged in the first period after the injection. Then, as the blood pressure falls and gradually returns to the control level, there is a decided shift of the maximum of the amplitude of the integrated potentials to the fourth group, i.e., to a higher frequency, and this shift to the "right" is accentuated by the fact that the amplitudes of the first three groups (particularly of the second and third) is decidedly decreased. This change is seen in the last four periods of the top record, whereas at the bottom record the return to

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* The pen deflection pips comprise the following frequencies per second: first group: 1.5, 2, 2.5, 3, 3.5; second group: 4 to 7; third group: 8 to 13; fourth group: 14, 15, 16, 18; fifth group: 20, 22, 24, 27, 30.

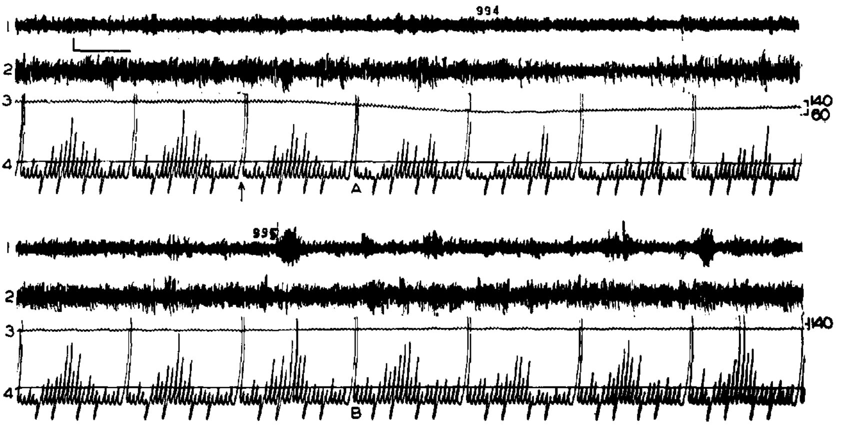

*Figure 90.* Effect of 5 gammas of acetylcholine (arrow indicates the injection) i.v. on the frequency analysis of cortical potentials. Note that after acetylcholine the last four records of analysis in *A* show a shift to the right. The maximal amplitude appears in the fourth group (at a frequency of 15/sec.) whereas in the preceding (first two records of *A*) and following control groups (*B*) it is in the third group (9 or 10/sec.), Nakao, Ballin, and Gellhorn (244).

*1.* Left motor cortex. *2.* Left auditory cortex. *3.* Blood pressure. *4.* Frequency analysis of site *1.* The records *A* and *B* are continuous. The calibration is 50 microvolts and 5 seconds.

the pre-injection pattern occurs.* The diminution in the amplitude of the integrated potentials at the lower frequencies and the increase in the integrated potentials at the higher frequencies during and immediately following the hypotensive phase are an indicator of the degree of excitation caused by the injection of acetylcholine.

Since acetylcholine may cause a direct excitation of the cortex of the brain (16, 238), either by local application or after intravenous injection, provided that the concentration is adequate or the destruction of the drug is prevented by eserine, it is important to prove that the excitatory effect is due to the action of the drug on the blood pressure and thereby on sino-aortic reflexes. For this reason, experiments were performed in which the effect of acetylcholine on the cortical frequency spectrum was studied before and after sino-aortic denervation.

A typical experiment is illustrated in Figure 91. In this graph the change in the amplitude of the integrated potentials which occurs after the injection of acetylcholine and particularly during the recovery of the blood pressure from the hypotensive level is expressed

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* In the lower record there is a "rebound" in the form of an accentuation of the grouped potentials which show up in the EEG and in the greatly increased amplitude of the potentials of the third group.

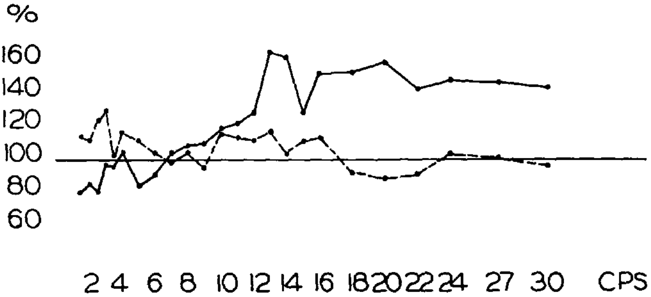

*Figure 91.* The influence of sino-aortic denervation on the action of acetylcholine on the occipital cortex of the cat, as indicated by the frequency analysis of the potentials. Note that acetylcholine causes a shift to the right, i.e., an increase in the amplitude of the potentials of a frequency of 10 to 30/sec. before denervation. However, this shift is absent after sino-aortic denervation, Nakao, Ballin, and Gellhorn (244).

The amplitude of four 10-second periods was averaged for each wave length and the results of the frequency analysis are expressed for each wave length in percentages of the control values. The solid line indicates the effect of 2 gammas/Kg acetylcholine i.v. before, the broken line the effect of 4 gammas of acetylcholine/Kg after sino-aortic denervation.

for each frequency in percentage of the amplitude recorded in the preinjection control periods. The graph shows that 0.002 mg/Kg of acetylcholine caused a slight reduction in that amplitude at low frequencies and a marked increase at the high frequencies when the sino-aortic receptors were intact. After denervation, however, acetylcholine, even in a dose of 0.004 mg/Kg failed to alter the frequency spectrum. From this and similar experiments it may be concluded that, when used in small doses, *the diffuse excitatory effect of acetylcholine (and other hypotensive drugs) on the cerebral cortex depends on the fall of the pressure in the sino-aortic area and the consequent release of the sympathetic centers, including those of the posterior hypothalamus.*

A final group of experiments remains to be reported. It was emphasized that hypotensive drugs lead to a diffuse cortical excitation and that this effect is reduced or abolished in the ipsilateral cortex by a unilateral lesion of the posterior hypothalamus. One would infer from these observations that the hypothalamus is essential not only to the restoration of the blood pressure from hypotensive levels, but also to the cortical activation paralleling such restoration. Therefore an effort was made to show that an excitation of the hypothalamus is associated with hypotension. Whereas it is rather easy to demonstrate the cortical excitation which follows the administration of hypotensive drugs (provided the anesthesia is sufficiently light), distinct changes of the

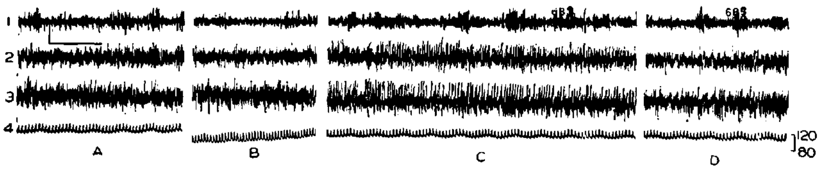

*Figure 92.* The effect of acetylcholine on a previously strychninized hypothalamus. Note that after recovery of the blood pressure from hypotension strychnine spikes develop in the hypothalamus.

Two hours before test 0.02 cc. of 0.5 per cent strychnine was injected into the right hypothalamus. *A.* Control. *B.* 12 seconds after 4.4 gammas/Kg acetylcholine had been injected i.v. *C.* 80 seconds after *B.* *D.* 75 seconds after *C.* *1.* Left hypothalamus. *2.* Right hypothalamus. *3.* Bilateral hypothalamus. *4.* Blood pressure. Calibration: 50 microvolts and 5 seconds.

hypothalamic potentials are difficult to obtain under these circumstances. If, however, the depressant effects of anesthetics are eliminated by light strychninization of the hypothalamus, the hypotensive drugs elicit the excitatory response quite clearly. This excitation appears in Figure 92 in the increased amplitude and frequency of the strychnine spikes as soon as the blood pressure returns from the acetylcholine-induced fall (*B*) to the control level (*C*). This effect is reversible (*D*). In addition, excitatory effects can be shown to occur in "light" animals even without the addition of strychnine. In such instances the frequency analysis of the hypothalamic potentials shows clearly an increase in the integrated amplitude of the relatively fast potentials. Since the analyzer is an integrating device, the records indicate that the total number of neurons discharging at a relatively fast rate has increased in the posterior hypothalamus during and after the recovery of the blood pressure from the drug-induced hypotension.

## 2. HYPERTENSIVE DRUGS AND THEIR RELATION TO THE HYPOTHALAMIC-CORTICAL SYSTEM

Whereas lowering the pressure with hypotensive drugs causes an excitation of the cerebral cortex, raising it by the injection of hypertensive drugs, such as noradrenaline or adrenaline, produces a diminution of cortical activity. If adrenaline is injected into a lightly anesthetized animal whose electrocorticogram is characterized by the absence of grouped ("dial") potentials, grouped potentials appear, as if a considerable amount of barbiturate had been administered. As Figure 93 shows, the grouped potentials remain confined to the period of hypertension, i.e., of increased sino-aortic pressure. The diffuseness of this effect and the character of the cortical changes suggest that an inhibition of the hypothalamic-cortical system is involved. Attention is

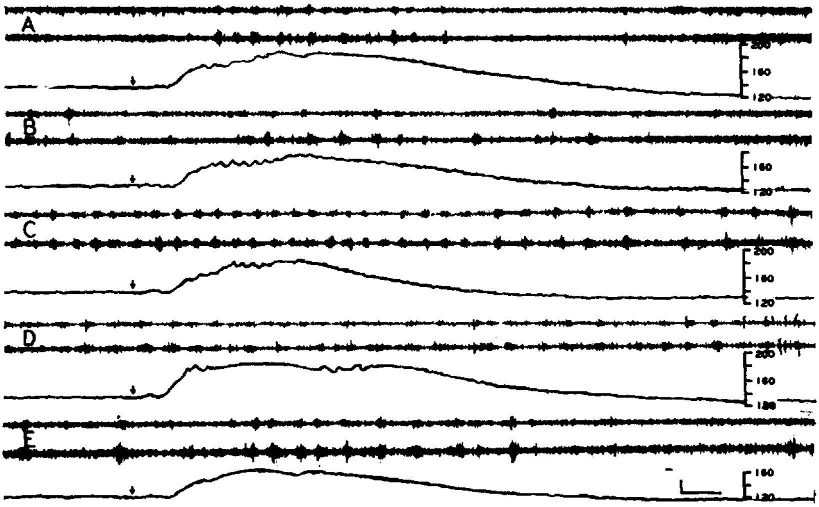

*Figure 93.* The effect of increasing barbiturate anesthesia on the action of adrenaline on the cerebral cortex. Note that the decrease of cortical excitability indicated by the augmentation of grouped potentials is present in the "light" cat and is abolished by barbiturates, Nakao, Ballin, and Gellhorn (244).

*1.* Gyrus proreus. *2.* Gyrus suprasylvius anterior. At arrows 10 gammas of adrenaline i.v. *A.* Control at 14:30; 2.8 mg/Kg sodium pentothal i.v., 14:42. *B.* 14:56; 2.8 mg/Kg pentothal 15:05. *C.* 15:18; 2.8 mg/Kg pentothal i.v. at 15:34, 15:50, 16:13. *D.* 16:18. *E.* 18:30. The calibration is 100 microvolts and 10 seconds.

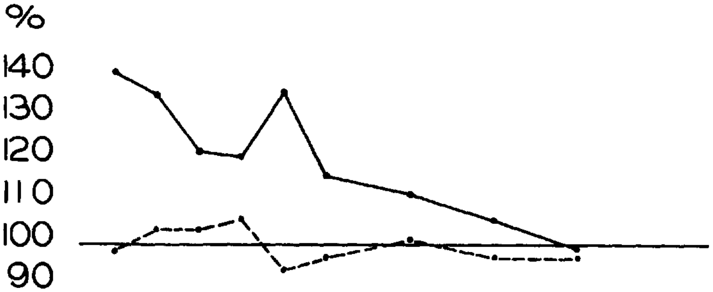

*Figure 94.* The effect of adrenaline on the cortical frequency spectrum before and after sino-aortic denervation. Note that adrenaline increases the slow potentials before but not after denervation, Nakao, Ballin, and Gellhorn (244).

The graph is based on experiments on 5 cats. Four to 6 gamma/Kg adrenaline i.v. before (solid line) and after (broken line) sino-aortic denervation. The integrated amplitudes of the potentials at varying frequencies obtained through an Offner amplifier were averaged before and after injection and the experimental effects were expressed as percentage of the controls for the frequencies 2 to 7.

called to the fact that small amounts of barbiturate diminish (*B*) and finally abolish (*C*) this action of adrenaline. These effects are reversible (*E*). This observation is interesting in view of the fact that the hypothalamic-cortical system, which is part of the reticular-thalamic-cortical system of Magoun, is highly sensitive to small amounts of barbiturates (6, 76, 96).

It was emphasized that hypotensive drugs cause a diffuse excitation of the cerebral cortex, which appears on analysis as a shift in the frequency spectrum toward the right (i.e., toward the higher frequencies). The appearance, when adrenaline was injected, of the grouped, i.e. of relatively slow, potentials suggested a shift of the frequency spectrum of cortical potentials to the left, and this assumption was verified experimentally. Figure 94 summarizes the experiments on five cats in which 0.0025 to 0.004 mg/Kg adrenaline had been injected intravenously. The graph shows that in cats with the sino-aortic receptors intact the record of the cortical analysis displays a progressive increase in the integrated amplitude of the cortical potentials as the frequency decreases from 7/sec to 2/sec.* If, however, the experiments are repeated after denervation of the sino-aortic area, adrenaline fails to alter the cortical frequency spectrum.

Similar experiments were performed with noradrenaline. As Figure 95 shows, a "shift to the left" in the cortical potentials similar to that described for adrenaline appears. The effect is likewise diffuse and occurs in the cerebral cortex as a whole. The action is bound to the sino-aortic receptors, since it is lost after surgical elimination of these receptors.

In some experiments, it is interesting to note, the sino-aortic denervation caused a reversal of the action of noradrenaline on the cortical frequency spectrum. In the normal animal this drug caused an increase in the amplitude of the integrated potentials at low frequencies (less than 10/sec) and this "left-shift" was sometimes aggravated by a corresponding diminution of the amplitude of integrated potentials with a frequency between 10/sec and 30/sec. After denervation an almost mirror-like change occurred: the potentials at low frequencies were diminished and those at high frequencies ($>$10/sec) were augmented in amplitude. Bearing in mind the fact that the "left-shift" accompanies a loss, and the "right-shift" an increase of excitation, it may be said that *hypertensive drugs induce through the reflex action of the baroreceptors a diminution of cortical excitability. Adrenaline and noradrenaline per se, i.e., after the elimination of the inhibitory*

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* There was no significant change in the integrated amplitude of the cortical potentials at frequencies higher than 7/sec.

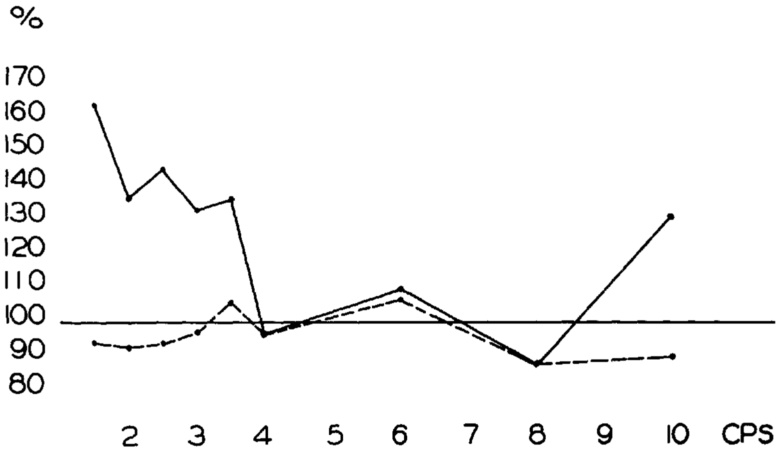

*Figure 95.* The effect of noradrenaline on the cortical frequency spectrum before and after sino-aortic denervation. Note that noradrenaline increases the slow potentials before but not after denervation.

Solid line before denervation and broken line after denervation. 2 gamma/Kg noradrenaline i.v. Five 10-second periods were analyzed. Motor area.

*action mediated by the sino-aortic receptors, may exert a diffuse excitatory action on the cerebral cortical potentials.*

## F. THE CORTICO-HYPOTHALAMIC DISCHARGE IN HYPOTHALAMIC IMBALANCE

The work presented in this chapter gives evidence that the hypothalamus, under strictly physiological conditions and also in a state of experimentally induced autonomic imbalance, exerts a great influence on the cerebral cortex. Important as the hypothalamic-cortical discharge is for the physiology and pathology of cortical functions, the hypothalamic-cortical relationship rests on a still broader basis, the mutual dependence of cortex and hypothalamus. Using the strychnine method of Dusser de Barenne (application of a minute piece of strychninized filter paper to some part of the cortex), Murphy and Gellhorn (242, 243) showed that strychnine discharges are conducted from various cortical areas to the hypothalamus and appear there as spike potentials. Ward and McCulloch (310) assumed that such a corticofugal effect on the hypothalamus was obtainable from the frontal lobe only, but a recent study (74)* on the monkey showed that strychnine discharges could be elicited from numerous cortical areas (oculomotor and sensorimotor cortex, certain parts of the parietal, occipital, and temporal lobes, etc.), the discharges appearing in various parts of the reticular system of Magoun, including the hypothalamus. It may therefore be said that the hypothalamus is influenced by impulses originating in a large section of the cerebral cortex. The anatomical pathways for fronto-hypothalamic discharges have been described by LeGros Clark (44).*

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* See also items 183, 222, 276.

Recently Bremer (28–30) has made valuable contributions to the problem of cortico-hypothalamic relations.† He has shown that acoustic stimulation awakens an unanesthetized cat in which the spinal cord has been transected below the medulla oblongata. This effect is abolished by destruction of the auditory cortex, although such an animal can be awakened by afferent impulses of cutaneous origin. Bremer assumed that impulses transmitted from the sensory projection area of the cortex to the reticular system initiate the reticulo-hypothalamic-cortical discharge that is associated with the awakening. Later he confirmed (and this is in agreement with previously cited work; see items 73, 242) that the reticular substance can be excited from various cortical areas. Such stimuli lead also to the typical EEG changes which accompany awakening—the slow potentials (spindles) are replaced by faster potentials of low amplitude (asynchrony); and eye movements and dilatation of the pupils appear at the same time.

After the corticofugal discharge to the hypothalamus and the reticular system had been well established through these investigations, an attempt was made to clarify further these relations and to evaluate them in conditions of hypothalamic imbalance of the autonomic nervous system.

In a group of experiments it was shown that if minute amounts of strychnine are injected into the cortex, regardless of whether the frontal or occipital grey mantle is selected, the posterior hypothalamus is excited.‡ The frequency analysis of the hypothalamus shows that the integrated amplitude of the potentials with relatively high frequencies is increased and the amplitude of the potentials with low frequencies is decreased. These effects may appear, as Figure 96 shows, in the absence of any convulsive potentials.

The excitatory action of the cortex (induced by the application of strychnine to the surface of the cortex or by the injection into the cerebral cortex of 0.02 cc. of 0.5 per cent strychnine) on the hypo-

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* For the important relation between the rhinencephalon and the hypothalamus, see items 220, 249, 254.

† Bremer emphasized the cortico-reticular relation, but the reader is reminded of the fact that the posterior hypothalamus is a part of Magoun's reticular system.

‡ Unpublished work with H. M. Ballin.

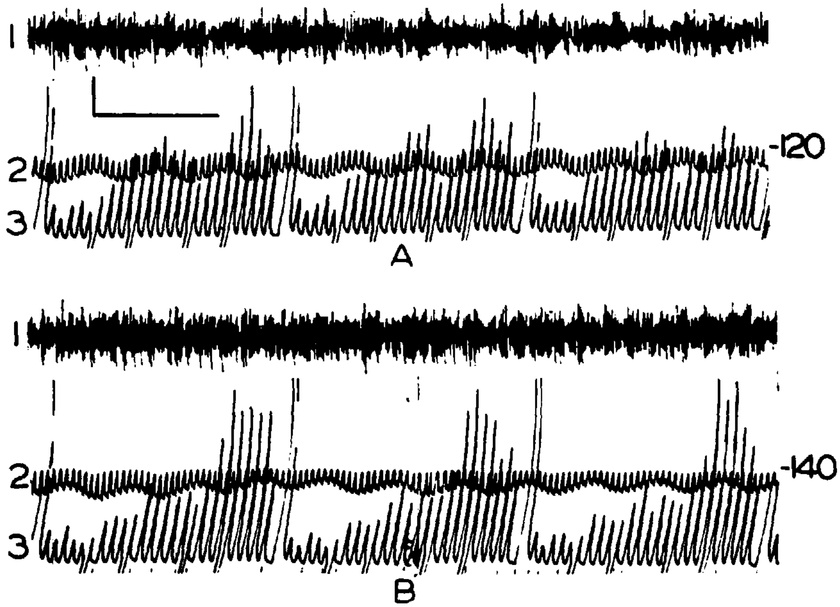

*Figure 96.* The influence of the injection of strychnine (0.02 cc. 0.5 per cent) into the left and right occipital cortex on the frequency analysis of the hypothalamus. Note that after injection (*B*) the potentials of low frequencies are diminished and those of high frequencies are increased indicating excitation of the hypothalamus.

*1.* Hypothalamogram. *2.* Blood pressure. *3.* Analysis of the record. Calibration: 50 microvolts and 5 seconds. *A.* Control. *B.* After strychnine in the cortex.

thalamus depends on the excitability of the hypothalamus. It appears in very "light" animals and also in cats in which a subthreshold concentration of strychnine has been injected into the posterior hypothalamus, and it is easily suppressed by barbiturates.

The conclusion drawn from these observations that corticofugal discharges elicited by a strychnine focus of the cerebral cortex cause an excitation of the hypothalamus is confirmed by the action of nociceptive stimuli. If the action of nociception on cortical and hypothalamic potentials is recorded under control conditions and after topical cortical strychninization, it is found that after strychnine the excitatory effect on the cortex and the diencephalon is increased in intensity and duration, as if an excitatory substance such as metrazol had been injected into the posterior hypothalamus.*

The problem of cortical and hypothalamic interaction and particularly the influence of the degree of activity of the posterior hypothalamus on corticofugal discharges was investigated further in two groups of experiments. Through a small pledget of strychnine applied to a certain cortical area, some local spikes were developed. Six electrodes were placed on the cortex at varying distances from the strychnine focus so that minimal to marked convulsive discharges were recorded. After strychninization a sufficient time was allowed for the potentials to become constant. Then the hypothalamus ipsilateral to the cortical strychnine focus was either strychninized or coagulated.

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* This finding is in agreement with the greater response of the brain stem to single sciatic shocks (74).

In the first group of experiments 0.02 cc. of 0.5 per cent strychnine was injected into the hypothalamus unilaterally, an amount which by itself had been found in control experiments to be inadequate to produce spikes in the ipsilateral cortex. This injection was effective in increasing the cortical strychnine discharge. In some experiments this increase appeared as an augmentation of the frequency and/or the amplitude of the spikes; occasionally it was found that an area which had been practically free from spikes before the hypothalamic injection showed them temporarily afterwards.

In the second group of experiments coagulation of the posterior hypothalamus or injection of pentothal into this structure was employed. Here the lessened hypothalamic activity caused a decrease in the frequency or amplitude of the strychnine spikes of the cortex.

These experiments demonstrate two important facts: (a) that the degree of excitation of the posterior hypothalamus and its reactivity to suitable stimuli (for instance, nociception) is increased by corticofugal discharges; (b) that the experimentally induced diminution or enhancement of hypothalamic excitability leads to corresponding changes in the intensity of the cortico-hypothalamic discharge indicated by the frequency and amplitude of the cortical strychnine discharges.

## G. EVALUATION

Among the experimental results presented in this section, the following important facts require some comment:

1. *Direct and reflex excitation of the posterior hypothalamus is associated with a diffuse excitation of the cerebral cortex. The intensity of this hypothalamic-cortical discharge is directly related to the excitability of the posterior hypothalamus.*

In earlier sections of this monograph it was shown that the hypothalamus plays an important role in circulatory and respiratory reflexes which were generally believed to involve only the spinal and medullary centers. The experiments described in this section indicate that the hypothalamus exerts, in addition, a profound influence on the cerebral cortex. This hypothalamic-cortical discharge is intimately related to the autonomic—"downward"—discharge, the intensity of which is relatively easily estimated by the mecholyl and noradrenaline tests.

Conditions which increase the sympathetic "downward" discharge lead likewise to an increased hypothalamic-cortical ("upward") discharge. This has been experimentally verified for such different procedures as hypothalamic stimulation, the inhalation of 10 per cent carbon dioxide, or the injection of drugs such as metrazol (administered either intravenously or by injection into the posterior hypothalamus). Similarly, if the sympathetic downward discharge is lessened by barbiturates (injected intravenously or directly into the posterior hypothalamus), by lesions confined to this structure, or by experimental hypothermia, the hypothalamic-cortical discharge is diminished. These alterations in the intensity of the hypothalamic-cortical discharge lead to typical changes in the cerebral potentials. Procedures that lower the excitability of the posterior hypothalamus produce an increase of the grouped potentials (spindles) in the cerebral grey matter. On the other hand, procedures that raise the excitability of the posterior hypothalamus cause an excitatory action on the cortical potentials (asynchrony, recruitment). In addition, the responsiveness to reflex stimuli such as nociceptive stimuli is lessened in the first case and magnified in the second. The intimate relation between the upward and downward discharges in a variety of experimental conditions seems to permit the autonomic tests revealing the intensity of the downward discharge to be used also as indicators of the reactivity of the hypothalamic-cortical system.

*2. The hypothalamic-cortical discharge is associated with the state of wakefulness. Conditions which interfere with this discharge cause somnolence and coma.*

This statement is based on the fact that coma results from lesions in the reticular formation of the midbrain. Under these conditions the impulses originating in this structure which are transmitted to the posterior hypothalamus and via the diffuse thalamic system to the cerebral cortex are greatly diminished. This diminution leads to a state of synchronization of the potentials of the cerebral cortex. On the other hand, awakening from light anesthesia is quantitatively related to the degree of activity of the hypothalamic-cortical system.

To understand the basis of consciousness and perception it is necessary to consider the following data: The diffuse and the specific afferent systems suffer unequally from deep barbiturate anesthesia; the activity of the former is completely suppressed, while that of the latter is preserved. The absence of consciousness and consequently of sensations and perceptions in anesthesia suggests that the evoked potentials of the specific sensory projection areas are not the physiological equivalents of sensations. Nor is the integrity of the reticulo-hypothalamic-cortical system adequate to maintain normal cortical reactivity, since animals in which the specific afferent system has been sectioned show a lessened response to afferent stimulation in spite of wakefulness and a normal EEG (215). Further experiments showed that in animals thus operated the response to sensory stimuli appears to be mediated by the collaterals of the specific afferent system to the reticular substance (289, 290), but the interaction between the two afferent systems resulting in quantitative (potentiation) and possibly qualitative effects on the cortex is no longer possible. It is believed that this interaction is essential for perception. To be aware without adding "of what" seems to be a rather meaningless statement. This content appears to be due to sensory impulses and, particularly in the higher organisms, to memory and other complex cortical events.

This interpretation of the basis of perception is supported by observations on cats in which hypothalamic electrodes had been inserted under nitrous oxide anesthesia. Two hours later the animals were awake, but their reactivity to environmental stimuli was often rather sluggish. Acoustic or optic stimuli too weak to evoke a reaction in them were easily chosen. When these stimuli were reapplied while the hypothalamus was excited with a weak stimulus which by itself produced only a slight reaction (dilatation of the pupils and contraction of the nictitating membranes), they elicited a typical sensory response: the animal turned its head toward the site of the acoustic stimulus or followed the light with its eyes.* A few seconds after the cessation of hypothalamic stimulation, however, these stimuli no longer evoked a sensory response. These observations indicate that perceptions are quantitatively (and possibly qualitatively) altered by changes in the intensity of the hypothalamic-cortical discharge.

3. *Variations of the blood pressure and consequently of the sino-aortic pressure alter the degree of the hypothalamic-cortical discharge, the latter being decreased as the pressure rises and vice versa.*

It has been suggested that the mechanism by which the variations of the blood pressure affect the activity of the hypothalamic-cortical system involves the baroreceptor reflexes of the sino-aortic area. After the elimination of the baroreceptors only minimal or no changes in cortical activity result from variations of the blood pressure that are very effective in the normal animal. Since with increasing pressure the discharges from the baroreceptors increase (32) while the activity of the posterior hypothalamus and the cortical grey matter is progressively diminished, it may be said that the baroreceptors restrain the activity of the sympathetic division of the hypothalamus. Here again one finds a parallelism between the "upward" and the "downward" discharge. Thus if noradrenaline raises the blood pressure, the degree of excitation of the whole cerebral cortex is lessened: grouped potentials appear, and the frequency analysis of these potentials shows a shift of the spectrum to the lower frequencies. On the other hand, the lessened sympathetic downward discharge—indicated by the fall of the blood pressure when the pressure of the isolated carotid sinus is raised—is associated with a lessened responsiveness of the sympathetic division of the hypothalamus to electrical stimulation.* At the same time the autonomic balance is shifted to the parasympathetic side ("parasympathetic tuning").

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*Reflex movements such as blinking of the eyes or movements of the pinna were likewise increased.

As far as the lowering of the blood pressure by acetylcholine or mecholyl is concerned, the diminished activity of the baroreceptors leads to a release of the posterior hypothalamus. Direct frequency analysis of the hypothalamic potentials indicates an excitation of the posterior hypothalamus. This excitation appears to be responsible for the increased hypothalamic-cortical discharges (asynchrony of the cortical potentials) and the increased reactivity of the hypothalamus to direct electrical stimulation. The raising of the blood pressure by noradrenaline calls forth the opposite changes in hypothalamus and cortex.

Although most of our experiments on hypotension were performed with mecholyl and related drugs, it should be mentioned that similar changes in the state of the hypothalamic-cortical system could be produced by varying the blood pressure through decreasing the circulatory blood volume. A cannula was inserted into the abdominal aorta, which was connected with a reservoir containing defibrinated blood. By changing the pressure in the reservoir below or above the level of the blood pressure, blood was made to enter or leave the circulatory system, with attending changes in the systemic blood pressure (69). When such experiments were performed on a cat with topically induced strychnine spikes of the cortex, changes in the spike frequency occurred similar to those seen on the administration of hypotensive drugs (as in Fig. 87). It is noteworthy that when the period of hypotension was extended to 25 seconds or more, the cortical spikes returned and reached an increased frequency in spite of the reduced level of the blood pressure. From these observations it seems to follow that the alterations in the frequency of the spike potentials are not simply due to corresponding changes in the cerebral blood flow.

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* See Chapter 1, Section B.

It was stressed earlier* that the mecholyl and noradrenaline tests depend on, and are a measure of, the excitability of the hypothalamus. Thus the interaction of the sympathetic discharges of hypothalamic origin and the reflex discharges of the sympathetic system resulting from hypotension (i.e., from the lessening of the firing of the baroreceptors) was assumed to be the basis of the mecholyl test. Now we can go even a step further. The baroreceptor impulses seem to restrain the posterior hypothalamus. Mecholyl reduces the blood pressure, thus diminishing the activity of the baroreceptors and consequently reducing their "restraint" of the posterior hypothalamus. Thus "released," the hyperactive posterior hypothalamus excites the cerebral cortex by an upward discharge and raises the blood pressure by a downward discharge. This release, other conditions being equal, will be more effective the greater the excitability of the hypothalamus. The different states of tuning which result from variations of the blood pressure † must also be interpreted on this basis.

4. *Corticofugal discharges contribute to the maintenance of the state of excitation of the posterior hypothalamus. The excitability of the hypothalamus, in turn, other conditions being equal, determines the degree of corticofugal discharge which results from a given cortical stimulus.*

Several types of experiments have shown that corticofugal impulses increase the rate of discharge of the hypothalamus and its responsiveness to various stimuli. Since conditions leading to a state of heightened excitability of the hypothalamus induce increased hypothalamic-cortical discharges, it may be said that increased corticofugal discharges cause also an augmentation of corticopetal (hypothalamic-cortical) discharges, the hypothalamus and the reticular substance of the midbrain having a key position in this circuit (positive feedback). It is obvious that if the excitability of the posterior hypothalamus is raised considerably either in experimental or clinical conditions, this circuit must lead to a tendency for this change to persist or to increase even further unless some homeostatic mechanism is called into play.

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* See Chapter 2, Section B.

† Whether the increase of the sino-aortic pressure affects the diencephalon only by diminishing the excitability and rate of discharge of the posterior hypothalamus and by reciprocally increasing the excitability of the anterior hypothalamus or whether a direct action on the latter occurs also has not yet been investigated.

## *Autonomic Imbalance and the Hypothalamus*

It was emphasized earlier that the hypothalamic-cortical discharge greatly increases the reactivity of the cortical projection areas to their specific afferent impulses and that the interaction of the specific and diffuse afferent systems is the basis of conscious sensations and perceptions. The experiments discussed in this chapter show that the hypothalamic-cortical relations are still more complex. Discharges originating in extensive areas of the cerebral cortex are directed to the hypothalamus (and the reticular substance) and have a profound influence on its state of excitability and thereby on all the complex functions (including the hypothalamic-cortical discharges) in which this structure plays an important part. Obviously if the posterior hypothalamus exerts such a profound influence on the susceptibility of the cerebral cortex to afferent impulses and also on the quantity and quality of the corticofugal discharges, it is not surprising that great disturbances in behavior may result from alterations in hypothalamic excitability.

The fact that cortico-hypothalamic impulses exist and that they influence the excitability of the posterior hypothalamus is of great interest as possibly providing a physiological understanding of the mechanism by which psychotherapy may alter hypothalamic functions and thereby emotional behavior.

CHAPTER 8

# EXPERIMENTS ON THE ACTION OF DRUGS ON THE HYPOTHALAMIC-CORTICAL SYSTEM

THE experiments discussed in the preceding chapters have shown that fundamental alterations in the reactivity of the hypothalamus are easily produced by physiological means and have far-reaching effects on the cerebral cortex. These studies were supplemented by some pharmacological observations. Although a complete survey of the action of drugs on the hypothalamus is beyond the scope of this book, some experiments are reported which show, at least in principle, how hypothalamic imbalances may be eliminated. The literature of the last years seems to indicate that science and industry will devote a great deal of effort to psychopharmacology and closely allied areas. The procedures used in the experiments described in this chapter may be useful for screening purposes and also for more detailed studies.

## A. OBSERVATIONS ON THE REACTIVITY OF THE HYPOTHALAMUS IN THE UNANESTHETIZED ANIMAL

A group of cats in which Dr. W. P. Koella had implanted electrodes in the posterior hypothalamus in an aseptic operation were subjected to numerous drug tests in subsequent weeks, before being sacrificed for histological studies. In these experiments the effect of electrical stimulation of the hypothalamus on the behavior of the unanesthetized cat and on the pupils, nictitating membranes, and heart rate was studied under the influence of various drugs.

Desoxyn was chosen as an example of a drug which exerts an excitatory effect on the hypothalamus. The injection of 1 mg/Kg intraperitoneally produced a distinct arousal reaction accompanied by signs of sympathetic excitation, such as marked or maximal dilatation of the pupils and piloerection on the back and neck. The pulse rate was not changed distinctly, but the respiration was increased. If the hypothalamus was stimulated at various intensities during this period of sympathetic excitation and the reactions were compared with those observed before the injection, it was noted that the arousal reaction and the sympathetic effects induced by hypothalamic stimulation were intensified or prolonged.

Similar experiments were performed with pentothal and chlorpromazine. Arousal reactions and the sympathetic effects of hypothalamic stimulation were found to be diminished with small doses of pentothal which did not alter significantly the behavior (posture, activity) of the cat. Chlorpromazine in doses of 10 mg/Kg (intraperitoneally) caused a reduction in the alertness of the animals (diminished response to environmental stimuli) and a slight lessening of the sympathetic responsiveness of the hypothalamus as indicated by the pupils, nictitating membranes, and the heart rate.

Clinical observations (218) based on the study of autonomic and psychological symptoms elicited by tetrahydronapthylamine suggested this drug as an indicator of central autonomic reactivity and balance. The effect of this drug on the hypothalamus was tested, therefore, on chronically operated cats. The experiments, however, failed to give any evidence that the drug acts on the hypothalamus.

Experiments of this kind seem to be useful to determine whether hypothalamic functions are altered by certain drugs or not. To obtain further insight, studies on the action potentials of the cortex and hypothalamus were carried out in acute experiments.

## B. THE ACTION OF BARBITURATES AND CHLORPROMAZINE ON CORTICAL AND HYPOTHALAMIC POTENTIALS

The first group of drugs studied was the barbiturates. If pentothal, nembutal, or Dial-urethane was injected into curarized cats while the action potentials were recorded from the cortex and hypothalamus, an increasing degree of synchrony was noted.* Grouped potentials of high amplitude appeared, and these changes were associated with a characteristic shift in the frequency spectrum:† the amplitude of the integrated potentials of a low frequency increased greatly so that the maximum of the analyzed record shifted to this group (shift "to the left" Fig. 97). The fundamental change in the frequency was particularly great in the cortical record. Before the injection of Dial-urethane a state of excitation prevailed, grouped potentials were absent, and the frequency spectrum showed the maximum at the right, or high-frequency, end of the spectrum. The hypothalamic record, however, showed already under control conditions a maximum at the left (that is, at low frequencies). Although the change caused by the drug was less in the hypothalamus than in the cortex, the type of change was similar in both areas.

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* Concerning the well-known action of barbiturates on cortical potentials and the EEG, see item 27.

† See p. 186.

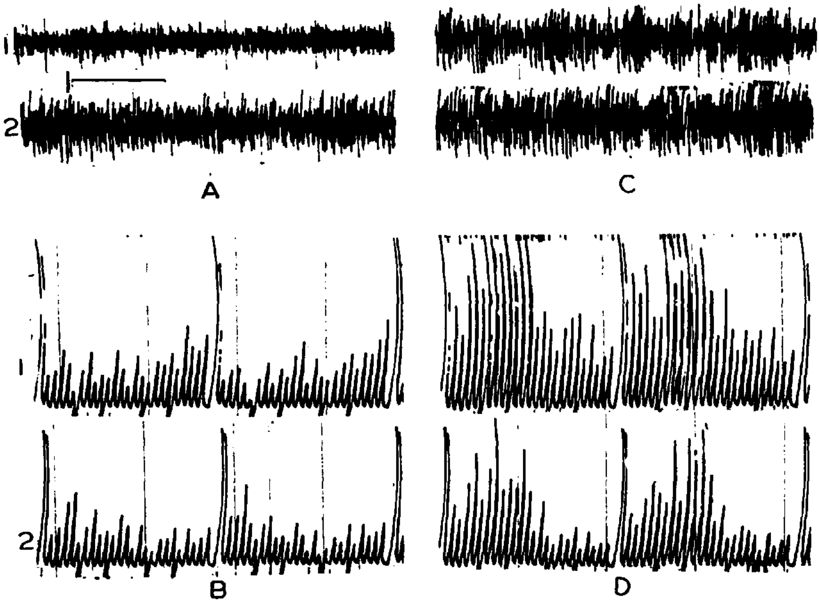

*Figure 97.* The effect of Dial-urethane on cortical and hypothalamic potentials. Note the marked increase in the amplitude of the integrated potentials at low frequencies (left part of each of the 10-second periods of the analyzed records shown in *D*) in cortex and hypothalamus after administration of the drug.

*A* and *B* before, *C* and *D* 5 minutes after 10 mg/Kg Dial-urethane had been injected intraperitoneally. *1.* Cortex. *2.* Posterior hypothalamus. The potentials recorded in *A* and *C* were analyzed in *B* and *D*. Calibration: 100 microvolts and 5 seconds.

When barbiturates were applied in small doses and the progressive changes were recorded in the cortex and hypothalamus, it was seen that before the final stage illustrated in Figure 97 was reached, a brief phase appeared in which cortical and hypothalamic potentials behaved quite differently. Whereas the cortical potentials showed the typical grouped pattern associated with a decrease in excitability and a shift in the frequency spectrum to the left, the hypothalamic (and also the thalamic) potentials showed an increase in frequency and amplitude but no spindles, and the hypothalamogram revealed a shift to the right. It is suggested that the depressing action of the barbiturates manifests itself first at the cortical and later (or with greater doses of the drug) at the hypothalamic level. In the intermediary state, in which the cortex but not the hypothalamus is depressed, the lessened activity of the cortex leads to a release of subcortical structures and thereby to changes in the action potentials which signify a state of increased excitation of the hypothalamus.

When during the final stage of the action of barbiturates the sympathetic and parasympathetic reactivity of the hypothalamus was tested either by electrical stimulation or by appropriate autonomic reflexes it was noted that both reactions were diminished. Figure 98 shows that the recovery of the blood pressure from the acetylcholine-induced hypotension was delayed and less complete after the injection of pentothal. The noradrenaline-induced slowing of the heart rate was also lessened (compare *B* and *E*). Since these reactions have been shown to depend on the excitability of the sympathetic and parasympathetic divisions of the hypothalamus, it may be said that barbiturates in small doses which do not lower the blood pressure diminish the autonomic reactivity of the hypothalamus. Records *C* and *F* of Figure 98 show also that the parasympathetic reflexes slowing the pulse rate in asphyxia were practically abolished after pentothal.

Similar investigations were performed with chlorpromazine. Pro-

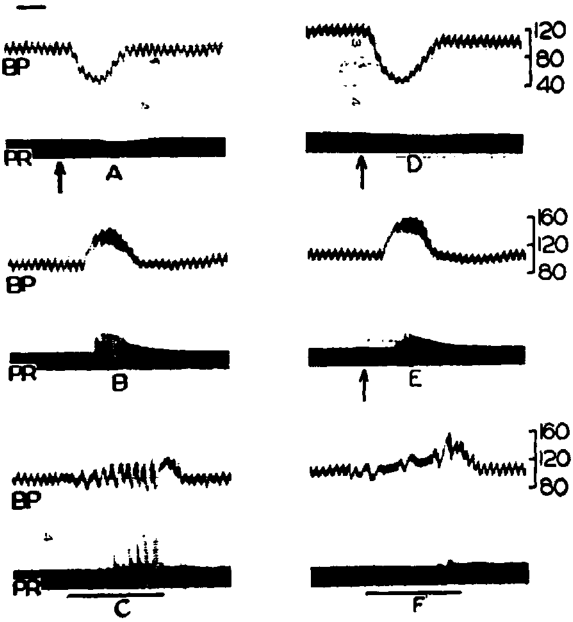

*Figure 98.* The effect of pentothal (i.v.) on the autonomic responsiveness of the hypothalamus as indicated by the acetylcholine, noradrenaline, and asphyxia tests. Note that after the administration of the drug the return of the blood pressure is delayed in the acetylcholine test and the pulse slowing in the noradrenaline and asphyxia tests is lessened.

*A* to *C* before, *D* to *F* after injection of 2 mg/Kg pentothal i.v. *A*, *D*, 3 gammas/Kg acetylcholine i.v. *B*, *E*, 0.8 gammas/Kg noradrenaline i.v. *C*, *F*, 40 seconds of asphyxia. Bar at the left upper corner = 12 seconds.

vided that they were carried out on very "light" animals, they gave results similar to those obtained with the barbiturates. In the cortical and hypothalamic control records of Figure 99 the grouped potentials were practially absent (*A*). After the administration of the drug they appeared slightly in *B* and were maximal at *C* in the cortex and hypothalamus at a time when the blood pressure had declined to an insignificant degree (from 164 to 150 mm. Hg). An analysis of the hypothalamic potentials showed the expected left shift.

There was also evidence that the action of chlorpromazine was greater on the cortex than on the hypothalamus and that the hypothalamus was released temporarily from cortical inhibition. When strychnine had previously been injected into the hypothalamus, the hypothalamic spikes increased in frequency at a time when, owing to the action of chlorpromazine, the cortex showed a marked depression (increase in grouped potentials).

The action of the barbiturates and of chlorpromazine showed further similarities. The effect of nociceptive stimuli on the cerebral cortex was lessened in both instances, a result which was expected, since this action on the cortex depends on the intensity of the hypothalamic-cortical discharge and thereby on the excitability of the posterior hypothalamus.

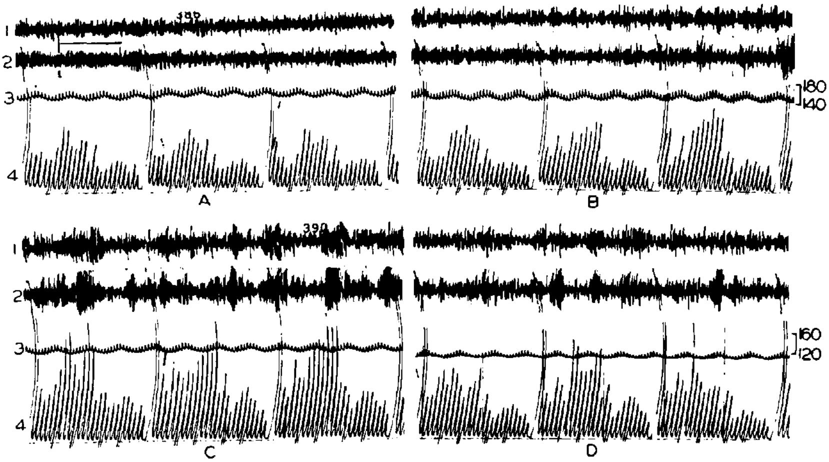

*Figure 99.* The effect of chlorpromazine on cortical and hypothalamic potentials. Note the appearance of grouped potentials in cortex and hypothalamus after the administration of the drug.

*A* before; *B*, *C*, *D*, 110 seconds, 130 seconds, and 20 minutes, respectively, after the injection of 3 mg. chlorpromazine/Kg i.v. *1*. Left posterior hypothalamus (bipolar recording). *2*. Bilateral motor cortex. *3*. Blood pressure. *4*. Analysis of the hypothalamic potentials recorded in *1*. Calibration: 100 microvolts and 5 seconds.

There were, however, great quantitative differences between the action of the barbiturates and that of chlorpromazine. Whereas it was very easy to produce grouped potentials in the cortex and hypothalamus with the barbiturates, this effect was often absent in experiments with chlorpromazine. Thus animals which had been prepared with small amounts of barbiturates often failed to show any changes in cortical (and hypothalamic) potentials upon the administration of chlorpromazine. On the other hand, cats prepared under ether and tested later reacted to chlorpromazine with an increase in grouped potentials. This is in agreement with the work of Hiebel *et al.* (167). It seemed to us that only animals in an unusual state of excitation showed a reduction in cortical and often also in hypothalamic excitability as indicated by the appearance of slow potentials.* When a barbiturate had been administered many hours earlier chlorpromazine failed to show an effect on the cortical potentials, although the appearance of the electrocorticogram (absence of grouped potentials) suggested a high degree of excitation.

From this work it is concluded that the barbiturates and chlorpromazine (for tests with the latter drug the cortex must be very much excited) depress first the cortex and then the hypothalamus.† By their action on the hypothalamus the drugs diminish sympathetic and parasympathetic responsiveness, as indicated by the acetylcholine and noradrenaline tests respectively, and lessen the reactivity of the hypothalamic-cortical system as measured by the action of nociceptive stimuli on the cerebral cortex.

## C. DRUG ACTION IN HYPOTHALAMIC IMBALANCE

It was shown earlier that a hypothalamic imbalance can be established by the injection of excitatory and anesthetic drugs into the hypothalamus. This method was used in order to determine whether states of hypothalamic imbalance can be abolished and the normal balance can be restored by drug action or other procedures.

Just a few examples may suffice to indicate the kind of results obtained in this work. In some experiments a sympathetic overreactivity of the posterior hypothalamus was produced by the injection of strychnine or metrazol into this structure. This resulted in a greater sympathetic response of the posterior hypothalamus to electrical stimulation than was obtained under control conditions and a more rapid return of the blood pressure from the mecholyl- or acetylcholine-induced hypotension. In addition, the nociceptive action on the cortex was increased. Any or all of these effects were easily abolished by the intravenous injection of pentothal or other barbiturates. As a matter of fact, the changes produced by small doses of barbiturates on these tests and also on hypothalamic and cortical potentials were even more striking than when barbiturates were studied in cats with unaltered hypothalamic functions.

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* The failure of chlorpromazine to alter the EEG of *resting* patients was explained by Shagass (278) on a similar basis.

† Heath (145) claims on the basis of electrical recordings in man that sodium amytal acts first on the subcortex and then on the cortex (as in normal sleep), whereas the sequence of action is reversed when phenobarbital is used.

Conversely, experiments were performed in which the excitability of the posterior hypothalamus had been lowered by the injection of barbiturates into this structure. In some of the experiments the preinjection reactivity of the hypothalamus to direct and reflex stimulation could be re-established by the intravenous injection of metrazol or strychnine in subconvulsive doses. The decreased responsiveness of the hypothalamic-cortical system was also eliminated by these procedures. An even more striking effect, similar to that of metrazol, could be obtained in conditions of diminished sympathetic hypothalamic reactivity by the inhalation of 10 per cent carbon dioxide. Desoxygen was likewise effective in counteracting a state of sympathetic hyporeactivity of the hypothalamus.

## D. THE CAUDATE NUCLEUS, THE RECRUITING RESPONSE, AND THE ACTION OF DRUGS

It was assumed that the alteration of the hypothalamic balance may change behavior because it leads to changes in the hypothalamic-cortical discharge and, consequently, in cortical activity. These quantitative changes in the hypothalamic-cortical discharge can be redressed by certain drugs which act on the hypothalamus and thereby modify these discharges. The cortex, however, receives impulses from the unspecific medial thalamic nuclei, which induce not only excitation but also inhibition. Such inhibitory effects have been produced by many authors (185, 240, 241) by stimulation of the thalamic intralaminar nuclei and of the caudate nucleus also.* Whereas stimulation of the reticulo-hypothalamic system produces an arousal reaction characterized by an asynchrony of cortical potentials, excitation of the thalamic nuclei or of the caudate nucleus with single shocks or stimulation at low frequencies calls forth cortical spindles similar to those seen in sleep. This "recruiting" response is obviously based on an increased synchrony of the cortical discharges.

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* Stimulation of the caudate nucleus in man reduces awareness so that drowsiness or a sleeplike state results (Heath, 144).

Although numerous questions need clarification, it seems not unreasonable to assume that the state of activity of the cortex as a whole or of extensive cortical areas depends, other conditions being equal, on the intensity of the physiological processes which activate these two systems. On the basis of this assumption two question are raised which seem to be important for the problem of the hypothalamic imbalance and its restitution: (a) How is the action of the inhibitory system altered in different states of arousal and hypothalamic imbalance? (b) How is the recruiting response altered by drugs which are known to affect the hypothalamic-cortical system?

In collaboration with Drs. Tokizane and Kawakami an extensive series of experiments was performed in which the threshold of the caudate nucleus for the elicitation of a recruiting response (spindle) in the cerebral cortex was determined in different states of arousal. Cats prepared under ether and local anesthesia were used for these experiments several hours later in the curarized state. Under these conditions states of drowsiness frequently alternated with states of alertness, as indicated by the transition in the EEG from periods showing spindles as in sleep to periods of small, frequent potentials. The application of single shocks to the caudate nucleus showed that the threshold for the recruiting response (spindle) rose distinctly during the alert phase and returned to the previous level in the subsequent drowsy phase. This result was confirmed in experiments in which the degree of alertness was increased by appropriate stimuli. Thus Figure 100 shows that the caudate-induced spindles disappeared during clicks

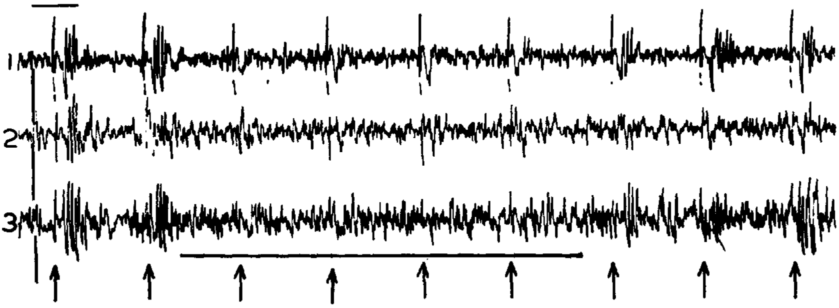

*Figure 100.* The effect of arousal by a noise (clicks) on the responsiveness of the caudate nucleus to single shocks. Note that the caudate-induced spindles disappear from the cortical records during the noise.

Cat prepared under ether, later flaxedil. The caudate nucleus was stimulated with single shocks (square waves, 7.0 v., 0.5 ms., every 2nd second, indicated by the arrow). The click noise (metronome) is indicated by the horizontal bar below the records. Calibration: 100 microvolts and 1 second.

produced by a metronome. Similar effects were produced by nociceptive stimulation, which is known to call forth an arousal reaction via the hypothalamic-cortical system, and by the electrical stimulation of the posterior hypothalamus or of the reticular formation.* The threshold of the caudate nucleus rose considerably under these experimental conditions. It may therefore be said that the inhibitory, spindle-producing action of the caudate nucleus is inversely related to the degree of activity of the reticulo-hypothalamic-cortical system, regardless of whether the activity of the latter is altered directly or reflexly or is the result of spontaneously occurring variations in hypothalamic activity.

The fact that carbon dioxide, as discussed earlier, increases the hypothalamic-cortical discharge considerably and that its action is readily reversible was utilized for the present problem. It was found that during hypercapnia the threshold for caudate-induced spindles rose in proportion to the concentration of the carbon dioxide used and to the duration of its application. Moreover, when the effect of carbon dioxide in establishing an alerting response of the EEG was prevented by barbiturate anesthesia, carbon dioxide failed to alter the caudate threshold. The important role of the state of the hypothalamus in these conditions is evident from the fact that the functional elimination of this structure by the injection of pentothal into the posterior hypothalamus or by high-frequency coagulation diminished or abolished the action of carbon dioxide on the caudate threshold.

The importance of the hypothalamic-cortical system for the effectiveness of the recruiting response elicited by stimulation of the caudate nucleus is evident also from the following pharmacological experiments. Metrazol on the one hand and pentothal and chlorpromazine on the other were chosen because these drugs are known either to increase or to decrease the excitability of the hypothalamus and thereby to alter the state of arousal correspondingly.

As Figure 101 illustrates, the threshold of the caudate nucleus for the cortical recruiting response (spindle) was raised upon the administration of metrazol. This effect was directly related to the concentration of metrazol and the degree and the duration of the arousal reaction.† The figure shows also that when the effect of metrazol on the EEG was prevented by the intravenous injection of pentothal, the threshold of the caudate nucleus for the elicitation of the recruiting response remained unaltered (*E*).

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* This experiment confirms the earlier work of Moruzzi and Magoun (241).

† The part of this figure showing that when metrazol evokes a convulsive discharge, the caudate stimulation becomes ineffective, need not be discussed here, since it is mainly of interest for the problem of convulsions.

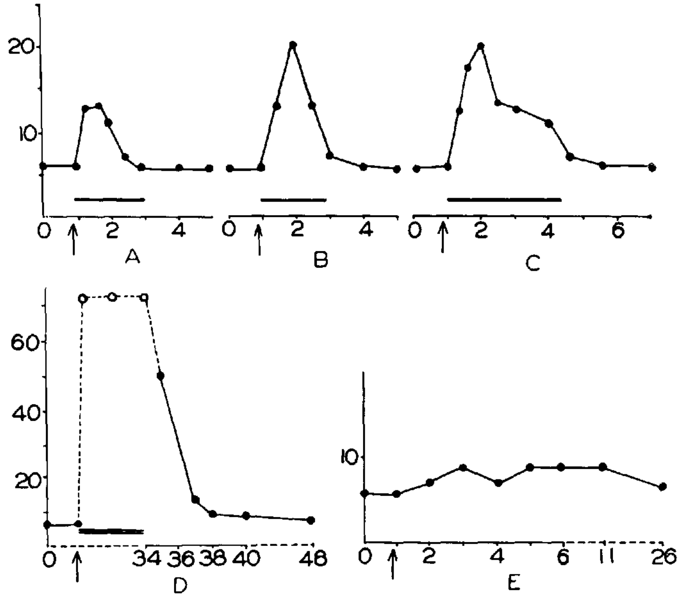

*Figure 101.* The effect of metrazol (i.v.) on the threshold of the recruiting response evoked by stimulation of the caudate nucleus. Note that the threshold of the recruiting response increases during metrazol-induced arousal and that this effect is abolished by pentothal.

Cat, 2.1 Kg., prepared under ether and flaxedil. Ordinate: threshold of the caudate-induced recruiting response in volts; abscissa: time in minutes. The experiments recorded in *A*, *B*, *C*, *D*, and *E* were performed at intervals of one hour. Metrazol (arrow) injected i.v.: *A*, 0.07 cc. (10%)/Kg; *B*, 0.1 cc/Kg; *C*, 0.15 cc/Kg; *D*, 0.17 cc/Kg; *E*, 0.25 cc/Kg. Two minutes before experiment *E* 5 mg/Kg pentothal was injected i.v. Solid line indicates cortical arousal; double line indicates convulsive discharges; line with dots indicates that the threshold was over 70 volts.

When drugs such as pentothal (see also item 192) or chlorpromazine were applied, the opposite effects were obtained. Even in doses too small to produce a significant change in the EEG, either drug lowered the threshold for the recruiting response. Moreover, the spindles produced by the threshold stimulus became more developed (in amplitude and duration).

Finally, the effect of panparnit* on the threshold of the caudate nucleus was investigated, since this drug diminishes the tone of the skeletal muscles and raises the threshold of proprioceptive reflexes (68). This action of panparnit seems to be due to a paralysis of the proprioceptor endings in the muscles and not to any action on the central nervous system. The drug was included in this series because of the great importance of proprioceptive impulses for the excitability of the posterior hypothalamus, which has frequently been emphasized.

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* It is also called parpanit. It is the diethylaminoethyl ester of phenylcyclopentane carboxylic acid.

In doses of 2 mg/Kg (i.v.) panparnit greatly lowered the threshold for the recruiting response. Since no experiments seem to have been performed on the action of this drug on the hypothalamic-cortical system, the question arose whether this change in threshold was likewise associated with an alteration in the state of arousal. Appropriate experiments showed indeed that under the influence of panparnit the threshold of the reticular formation for eliciting an arousal reaction was raised. Similarly, it was found that the arousal effect of nociceptive stimulation was lessened by panparnit. Apparently, panparnit lowers the threshold for the caudate recruiting response in doses which diminish the responsiveness of the hypothalamic-cortical system.

The experiments involving metrazol, pentothal, chlorpromazine, and panparnit confirm the conclusion derived from the physiological work on the stimulation of the caudate nucleus. Physiological or pharmacological conditions which lead to a state of increased excitability of the posterior hypothalamus and consequently to an increased hypothalamic-cortical discharge lead to a lessened effectiveness of the recruiting response: The threshold for eliciting this response by electrical stimulation of the caudate nucleus is raised. On the other hand, factors which diminish the excitability of the posterior hypothalamus and produce drowsiness increase the effectiveness of the stimulation of the caudate nucleus and lower its threshold. The intimate relation existing between the two systems is apparent from the fact that the reduction in function of the posterior hypothalamus by the intrahypothalamic injection of pentothal or by coagulation minimizes or abolishes the action of physiological and pharmacological agents which otherwise change the threshold of the caudate nucleus for eliciting the recruiting response.

## E. EVALUATION

The experiments described in this chapter were mainly designed for studying the effect of drugs on those hypothalamic functions which are related to the action of the hypothalamus on the cortex (upward discharge) and to the responsiveness of the hypothalamus to direct and reflex stimulation, as indicated by the blood pressure, heart rate, and nictitating membrane. It was shown that barbiturates and chlorpromazine decrease the sympathetic responsiveness of the posterior hypothalamus and diminish also the upward and downward discharges. Metrazol, strychnine in subconvulsive doses, and, in some instances, desoxyn exert the opposite effect. It is important to mention that a significant decrease (increase) in the excitability of the posterior hypothalamus produced by these drugs is invariably accompanied by a decrease (increase) in the upward and downward discharges. This parallelism makes it permissible to infer from one test the direction of the changes in related hypothalamic functions which have not been determined directly. Thus, if an experimental animal or a patient, as the result of the application of a drug, shifts from Group III to Group I* in the mecholyl test, indicating an increased sympathetic responsiveness of the hypothalamus to baroreceptor reflexes, it seems permissible to assume that the hypothalamic excitability to direct stimulation and the upward discharges are increased at the same time.†

It follows from these findings that if an attempt is made to restore the hypothalamic balance in clinical cases of autonomic imbalance, the restitution of function would not be restricted to the diencephalon but would alter cortical functions via the hypothalamic-cortical discharge. Consequently, changes in complex cortical functions and thereby in behavior are to be expected.

It should be understood that the drug experiments described in this book were not meant to be more than models to elucidate the principles by which the hypothalamic balance can be altered and restored and to show the effect of such alteration for cortical functions and the reactivity of autonomically innervated organs. By no means is it suggested that the drugs which, for instance, restore a hypothalamic imbalance characterized by a deficient sympathetic responsiveness are suitable for the treatment of clinical cases with a similar autonomic disturbance. Obviously, the drugs involved have numerous side effects which may not appear on the limited number of indicators used in our experiments. The suitability (and the successfulness) of a therapeutic procedure can be determined by clinical methods only, but the theoretical sciences can give direction to clinical endeavors through an experimental analysis.

One special point may still be mentioned. It was noted that the barbiturates and chlorpromazine act primarily on the cortex; only with higher doses or longer duration of the action of the drugs does the hypothalamus become depressed. This observation is, of course, in agreement with the differential susceptibility of the various levels of the cerebrospinal system to changes in the internal environment (oxygen, blood sugar, etc.). It may, therefore, be difficult to find drugs which react specifically upon the hypothalamus!

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* See p. 230.

† The reader is reminded of the previously discussed work showing that the parallelism between the various groups of hypothalamic functions was retained when hypothalamic functions were altered by the inhalation of carbon dioxide, by stimulation of the posterior hypothalamus, by the injection of drugs into the posterior hypothalamus, or by the production of lesions in this area.

It seems important to emphasize the fundamental difference between the barbiturates, which readily decrease the reactivity of the hypothalamus and reticular formation, and thereby eliminate consciousness and induce anesthesia, and chlorpromazine, which induces not more than a drowsy state or light sleep.* Courvoisier (47) showed that chlorpromazine readily abolishes conditioned reflexes but that barbiturates have no effects aside from their hypnotic action. This finding suggests, in the light of Pavlov's work, a close affinity between chlorpromazine and cortical functions. Such affinity is suggested also by the direct relation between the effectiveness of chlorpromazine in producing sleep and the development of the cerebral cortex in different species (13) and by the recent ingenious experiments of Brady (25).

The action of chlorpromazine does not remain confined to the cerebral cortex, since the drug may produce grouped potentials in the posterior hypothalamus. This effect is slight, and it is therefore not surprising that it does not prevent the action of massive stimulation of the hypothalamus in mobilizing ACTH from the anterior hypophysis (175). The drug is effective, however, in shortening manic attacks and ameliorating states of anxiety (13, 195, 210). Since corticofugal impulses to the hypothalamus (243) and the reticular substance (30, 74, 183, 268) contribute importantly to their state of activity, it is suggested that the lessened reactivity of the hypothalamus after the administration of chlorpromazine is due to a diminution of the cortico-hypothalamic impulses.† On the basis of this analysis it is tentatively proposed that hypothalamic imbalances may be redressed also by drugs which act on the cortex and thereby alter the rate of the cortico-hypothalamic discharge. Drugs causing a diminution of cortico-hypothalamic impulses are apt to counteract sympathetic hypothalamic hyperreactivity, whereas drugs increasing these impulses should tend to restore the hypothalamic balance in cases of sympathetic hyporeactivity.

Our experiments on the action of drugs on the recruiting system failed to reveal any drug action specifically affecting the recruiting response elicited by the stimulation of the caudate nucleus. Instead, they gave further evidence of the importance of the hypothalamic-cortical system. It was surprising to find that physiological conditions such as those produced by the inhalation of carbon dioxide or the administration of excitatory drugs like metrazol (in subconvulsive concentrations), which increase the reactivity of the posterior hypothalamus to only a moderate degree, greatly diminished the responsiveness of the recruiting system. One might have thought that an increase in the rate of discharge of the hypothalamic-cortical system would be offset by a similar increase in the reactivity of the recruiting system, but evidence for such a homeostatic mechanism could not be found.*

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* Baruk and his coworkers (13) observed catalepsy with high doses of chlorpromazine. It remains to be seen whether this effect is not due to the fall of the blood pressure.

† The reflex response to proprioceptive stimuli is said to be diminished by chlorpromazine in human spastics (14). It is conceivable that this diminished effectiveness of proprioceptive stimuli contributes to the loss in hypothalamic reactivity (see Chapter 4).

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* See Chapter 13 for a further discussion of this problem.

# *PART II. REVIEW OF RESULTS AND CLINICAL APPLICATION*

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CHAPTER 9

# THE EXPERIMENTAL FOUNDATION AND THE CLINICAL APPLICATION OF THE CONCEPT OF PARASYMPATHETIC AND SYMPATHETIC TUNING OF THE AUTONOMIC NERVOUS SYSTEM

IN CONTRAST to the somatic nervous system the autonomic system shows a rather irregular behavior under a variety of conditions. Even in the simple nerve-muscle preparation the effect of the stimulation of a nerve is variable inasmuch as it depends on the state of the muscle. Vagal stimulation leads to an increase in the tone and contraction of the stomach if the state of activity of this organ is low, but to an opposite effect if the spontaneous activity is considerable. Other factors may likewise alter the reactivity of an autonomically innervated organ to nervous stimulation. Thus, the response of the uterus to stimulation of the hypogastric nerve is different in the virginal and in the pregnant state, and the reactivity of the blood vessels to sympathetic stimuli depends on the chemical environment in which the experiment is performed. Since differences have frequently been observed clinically between the reactions to a given stimulus (condition of stress) that patients in apparently similar conditions, or the same person in different situations, will give, it seems likely that an investigation of the mechanisms underlying the *central* modifiability of autonomic reactions may contribute to an understanding of physiological reactions and of related clinical problems also. For this reason autonomic reactions were studied in experimental animals (cats) in which the balance of the autonomic system had been shifted to the sympathetic or the parasympathetic side. In the former case we speak of sympathetic, in the latter of parasympathetic, tuning.

## A. REVIEW OF PHYSIOLOGICAL EXPERIMENTS

With the blood pressure and heart rate and the sympathetically innervated nictitating membrane serving as indicators of the autonomic system, an alteration in the autonomic balance was accomplished in most experiments by changing the blood pressure through the action of drugs, thereby eliciting reflexes from the baroreceptors of the sino-aortic area. When a hypotensive drug (mecholyl, acetylcholine, or histamine) is injected intravenously, the fall of the blood pressure and consequently of the sino-aortic pressure calls forth a shift in the autonomic balance to the sympathetic side. This is due to the lessened discharges from the sino-aortic receptors which through their reflex action restrain the central sympathetic structures. This shift of the autonomic balance to the sympathetic side is referred to as "sympathetic tuning." From the acceleration of the heart rate and the contraction of the nictitating membrane which occur as the blood pressure recovers from the drug-induced hypotension it is evident that in this state the central sympathetic discharges are increased.

In such a state of sympathetic tuning the autonomic system was tested with stimuli which either reflexly or directly evoke a sympathetic effect. Stimulation of the sciatic nerve was chosen for the reflex type, excitation of the posterior hypothalamus for the direct. The results were the same in both cases: the sympathetic effect of stimulating the sciatic nerve and the posterior hypothalamus was greater in the state of sympathetic tuning than in the preceding and following control conditions. This change in sympathetic reactivity was indicated by the greater contraction, in response to the stimulus, of the nictitating membrane and/or the increased acceleration of the heart rate (see Figs. 5–7).* The effect was obtained with any of the three hypotensive drugs which were studied. How powerful the tuning effect was is evident from the fact that it occurred even when the hypotensive drug was applied in concentrations too small to evoke a sympathetic reaction of the nictitating membrane. In other words, a state of sympathetic tuning which did not lead to overt sympathetic effects nevertheless increased sympathetic reactivity!

Similar states of sympathetic tuning could be induced by lowering the blood pressure (and consequently the sino-aortic pressure) through other means. Thus it was found that hemorrhage or sciatic stimulation (provided that the latter utilized low frequencies and thereby elicited parasympathetic effects on the blood pressure) led to an increased sympathetic responsiveness, as evidenced by the effect of stimulating the posterior hypothalamus. *Since after sino-aortic denervation the effect of sympathetic tuning no longer occurred when hypotensive drugs were injected (Figs. 20–21), it may be said that under these conditions the sympathetic tuning is the result of an alteration in central sympathetic reactivity through sino-aortic baroreceptor reflexes.*

A state of parasympathetic tuning could be attained in a corresponding manner. When the blood pressure (and thereby the sino-aortic pressure) was raised, an increased responsiveness to parasympathetically acting stimuli was accomplished. Thus a hypothalamic stimulus which elicited a minimal parasympathetic effect under control conditions (very slight fall of the blood pressure and heart rate; see Fig. 8) caused a much greater parasympathetic action when it was applied during the state of parasympathetic tuning induced by the rise of the blood pressure upon the injection of noradrenaline. Here again the nature of the drug was immaterial provided it led to an increase in the sino-aortic pressure (see Fig. 9). Moreover, the effect was abolished by denervation of the sino-aortic area (Fig. 22). If the blood pressure was increased by the injection of blood or dextran, a state of parasympathetic tuning resulted likewise.

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* See note on p. 11 for explanation of the figures.

Further investigations showed that both divisions of the autonomic nervous system were influenced by the state of sympathetic and parasympathetic tuning. During sympathetic tuning the reactivity of the parasympathetic system was found to be less than under control conditions (Fig. 14). Conversely, the action of a sympathetically acting stimulus was lessened during the state of parasympathetic tuning (Figs. 10–12). *It follows from these experiments that the principle of reciprocal innervation remains valid under the conditions of a reflexly altered autonomic balance.*

The mechanism involved in the characteristic changes in autonomic reactivity observed in states of tuning is simple. It is based on summation processes. When two sympathetically acting stimuli were studied in their effect on the blood pressure, heart rate, and nictitating membrane singly and also in combination, in combination the action was seen to be greater than corresponded to the algebraic summation. This *potentiation* was particularly striking when one of the stimuli chosen was so slight as to be ineffective altogether or at least to be without effect on any of the indicators used in the experiment. Thus when of two hypothalamic stimuli one did and the other did not elicit a contraction of the nictitating membrane, the effect of the two in combination was more than doubled (Fig. 1). Similarly, it was found that parasympathetically acting stimuli summate and show also the phenomenon of potentiation (Figs. 3, 4).

The application of these findings to the state of tuning is obvious. If through an appropriate stimulus a state of sympathetic tuning is reflexly produced, the sympathetic discharges in this state are greater than under control conditions.* Consequently, a sympathetic test stimulus produces a greater sympathetic effect during sympathetic tuning than when applied during a state of "normal" autonomic balance and, obviously, this explanation accounts for the greater effectiveness of parasympathetic stimuli in the state of parasympathetic tuning. But we can go even further. It is well known that if we lower the sino-aortic pressure, sympathetic discharges are increased and parasympathetic discharges are diminished. Since the action of the test stimulus is determined by the summation processes resulting from its own action and the autonomic reflex discharges present at that time, it is evident that a parasympathetically acting test stimulus will summate, in the state of sympathetic tuning, with fewer parasympathetic reflex discharges than in a state of normal autonomic balance. Hence the action of a parasympathetic stimulus is lessened in a state of sympathetic tuning, and that of a sympathetic stimulus is lessened in a state of parasympathetic tuning.

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* This statement seems to be correct even for a state of sympathetic tuning that, because of its subthreshold character, gives no direct evidence of increased sympathetic discharges.

In order to give a wide application to these investigations, other forms of autonomic tuning were studied. Instead of lowering the sino-aortic pressure, one may establish a state of sympathetic tuning by means of nociceptive stimuli (electrical stimulation of the central end of the sciatic nerve or immersion of the tail in hot water) or by stimulation of the posterior hypothalamus. Similarly, a state of parasympathetic tuning may be established either by applying a stimulus of low frequency to the sciatic nerve or by stimulating the anterior hypothalamus. Such experiments were performed with subthreshold and suprathreshold intensities of stimulation, and the rules outlined above concerning the reactivity of the autonomic system in states of tuning were found to be valid.

Finally, it was found that changes in the internal environment produced reversible alterations in the state of autonomic tuning. Thus a state of sympathetic tuning occurs in asphyxia. Following a *prolonged* asphyxia (more than 80 seconds), states of sympathetic and parasympathetic tuning were observed in which the characteristic changes in autonomic reactivity could again be demonstrated.

The changes in the reactivity of the autonomic system as the result of sympathetic or parasympathetic tuning go even further: they lead to qualitative changes, illustrated in the phenomenon of reversal. In the condition of parasympathetic tuning induced by the injection of noradrenaline, a stimulus acting sympathetically under control conditions (whether a nociceptive one or an electrical stimulus of the posterior hypothalamus) produced parasympathetic effects: instead of a rise of the blood pressure and an acceleration of the heart rate, a fall of the blood pressure and heart rate appeared (see Figs. 10 and 18).

The mechanism underlying this phenomenon of reversal seems to be based on summation processes which are altered characteristically in states of autonomic tuning. It can be shown that stimuli apparently acting only on the sympathetic system actually cause an excitation of both divisions of the autonomic nervous system. The effect on the sympathetic division, however, dominates and obscures the action on the parasympathetic under control conditions. If this is the case, it is easily understandable that in a state of parasympathetic tuning sympathetic excitability is decreased and parasympathetic increased so much that a parasympathetic effect is produced in response to a stimulus that in a state of normal autonomic balance produces a sympathetic effect.

Although the alteration in the reactivity of the autonomic nervous system has been discussed thus far for states of reflex tuning, it should be stressed that central autonomic imbalances lead to similar states of tuning. They were attained by altering the excitability of the anterior or the posterior hypothalamus directly.* The previously stated simple rules of autonomic "tuning" apply likewise to this group of experiments.

## B. APPLICATION

Ever since Eppinger and Hess (64) discussed the vagotonic complex, attempts have been made to describe and classify central autonomic disturbances. According to the German and Austrian medical literature (22, 83, 143, 232)—apparently not duplicated in the Anglo-American literature—such cases were very common during the emotional upheaval of the war and post-war years. States of sympathetic hypertonia have been described which seemed to be characterized by differences in the basal sympathetic tone and by the heightened reactivity to sympathetically acting stimuli. Autonomic reflexes may be reversed: pressure on the eyeball causes an acceleration (instead of a slowing) of the heart rate. In these respects the patients show some of the fundamental features seen in the experimental animal after the injection of metrazol into the posterior hypothalamus. Similarly, states of sympathetic hypotonia in human beings may be likened to conditions in the experimental animal resulting from the injection of pentothal into, or lesions of, the posterior hypothalamus.

Cases of hypertonia of the parasympathetic system show low blood pressure and heart rate, and increased motor and secretory activity of the gastrointestinal tract. The increased hypoglycemic phase following a glucose tolerance test may be interpreted as increased reactivity of the vago-insulin system. I refrain, however, from a further discussion because of lack of personal experience, but a *critical* reinvestigation of the diagnostic and therapeutic* problems in the light of the experimental work presented in this book is suggested.

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* See Chapter 2, Section B.

The important investigations of Losse *et al.* (217) appeared as this book was going to press. By applying multiple circulatory, metabolic, and blood tests they found that among healthy persons a small group (8 per cent) showed, when compared with the majority, an increase in the blood pressure, heart rate, minute volume of the heart, and oxygen consumption and a decrease in the number of lymphocytes and eosinophiles, whereas another group of similar size showed the opposite behavior. The former represents the sympathotonic and the latter the parasympathotonic group, whereas the bulk of normal persons are found in an autonomically mixed group. The groups are related to the body structure and depend chiefly on genetic factors, since the autonomic types of identical twins (but not of fraternal twins) are similar. Cases of hypertension and gastric ulcers showed an increased tone of the sympathetic and parasympathetic systems respectively. The differences between the "normals" and the clinical cases with autonomic disturbances are quantitative rather than qualitative. Our studies on the mecholyl test in normals and psychotics (Chapter 10) lead to a similar conclusion.

Whether or not the various types of central autonomic disturbances should be regarded as well-defined nosological entities (171), it can hardly be doubted that changes in autonomic reactivity occur during emotional tension and find their expression in characteristic autonomic patterns. The interindividual variations in the behavior of the nasal mucosa (172, 320) and the vascularity of the face (267) suggest that in some persons the autonomic balance and reactivity is shifted to the sympathetic side whereas in others the parasympathetic system dominates. The performance of a standard exercise during emotional tension causes a greater increase in the blood pressure and stroke volume, in addition to certain respiratory changes, than is observed when the subject is in a relaxed state. On the other hand, in a state of despair and discouragement the heart rate and cardiac output may, during a standard exercise, fall below the resting level (59, 319–321).

Hypertensives show during a "stressful interview" a greater renal vasoconstriction than normotensive subjects (321). There can be little doubt that under the influence of repeated emotional stresses the central autonomic balance may become altered for longer periods of time or permanently. Such alterations may contribute to the development of diseases like hypertension and Raynaud's disease (frequently associated with emotional disturbances (134), in which the sympathetic downward discharge is increased. A similar relation seems to exist between ulcers and certain parasympathetic reactions, resulting in an increased vascularity and secretion of the gastrointestinal system during states of hostility (Wolf and Wolff). It is very probable that frequent emotional disturbances may lead to central autonomic imbalances, with consequent changes in the hypothalamic-cortical discharge.* The beneficial effect of muscular relaxation in cases of increased upward or downward discharges seems to be based on the fact that proprioceptive impulses have a strong influence on the excitability of the posterior hypothalamus† and thereby on the intensity of upward and downward discharges.

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* See Hauswirth's suggestive but uncritical data (143).

It has frequently been noted in our studies that the effect of tuning is more marked on one organ than on another. Depending on the site and intensity of the hypothalamic test stimulus, for instance, the effect of sympathetic tuning may appear as an increased response of the blood pressure or the heart rate or the nictitating membrane, or it may be present on all three indicators. These experiments are in agreement with the observations of Wolff (324) that an emotional stimulus causes autonomic effects in specific parts of the body. Depending on this site Wolff speaks of "stomach reactors," "pulse reactors," "nose reactors," etc. In addition I suggest that segmental autonomic reflexes increase the reactivity of a certain organ specifically so that it reacts to hypothalamic (emotional) discharges more than do other parts of the body.‡

Studies of the blood sugar in emotional conditions furnish data on the reversal of autonomic reactions. Whereas emotional excitement causes a rise of the blood sugar in the normal person, it frequently fails to change the blood sugar level in psychotic patients (24, 131, 316). In certain neurotics emotional tension may produce significant degrees of hypoglycemia (252, 264). The mechanism involved in this reversal seems similar to that proposed earlier in explanation of the vascular reversal phenomenon. It was shown that emotional excitation leads to an adrenomedullary secretion via the splanchnics and also to the secretion of insulin via the vagus nerves (98, 106, 113). Whereas in the normal person the sympathetico-adrenal discharge outweighs the vago-insulin discharge, the balance is altered or even reversed in those cases in which emotional excitement fails to change the blood sugar or produces hypoglycemia. The observation (306) that in about 25 per cent of schizophrenic patients electroshock causes a fall of the blood sugar instead of the usual rise suggests a similar interpretation.*

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* See Chapter 7.

† See Chapter 4.

‡ Another mechanism which may account for different states of tuning in different organs is illustrated in Figure 13.

Wilder (317) has shown that the higher the initial level of a function the less is the tendency toward a further increase and the greater the tendency toward a diminution of it. Applied to the blood pressure, his studies suggest that stimuli which increase the pressure when administered in a state of hypotension, may decrease it when applied in a state of hypertension. Although there is a considerable literature in support of Wilder's findings (see, for instance, item 328), quite obviously this explanation cannot account for the phenomenon of reversal under discussion for the following reasons: (a) If the blood pressure is raised from 100 mm. Hg to 130 mm. Hg by stimulation of the posterior hypothalamus in one experiment and by the injection of noradrenaline in another, the reaction of the blood pressure to a certain sympathetically acting stimulus (test stimulus) is quite different in the two experiments. The test stimulus raises the blood pressure more than under control conditions in the first experiment, whereas it causes a fall (reversal) in the second experiment. The reason is that the state of central autonomic tuning is different in the two experiments although the initial level is the same. (b) Persons that fail to show a change in the blood sugar under emotional stress or develop hypoglycemia do not show higher initial blood sugar levels than normal persons, who respond to such conditions with hyperglycemia. Wilder's assumption would require such differences.

*If the restraining action of the carotid sinuses is eliminated by denervation or infiltration with novocaine, the sympathetic "centers" are in a state of hyperreactivity as shown by the hypertension which results from this procedure. The recent observation that the hypoglycemic action of insulin was reversed into a hyperglycemic effect after functional elimination of the carotid sinuses by novocaine (291) is possibly related to this change in the central autonomic balance. This reversal may be due to the increased responsiveness to insulin hypoglycemia of the sympathetico-adrenal system in this state of reflexly increased hyperreactivity of the sympathetic "centers." The repetition of this experiment in animals before and after adrenodemedullation should clarify this question.

CHAPTER 10

# THE EXPERIMENTAL FOUNDATION AND THE CLINICAL APPLICATION OF THE MEASUREMENT OF HYPOTHALAMIC IMBALANCE IN THE INTACT ORGANISM

## A. REVIEW OF EXPERIMENTAL RESULTS

THE experimental work discussed in the preceding section showed that through reflexes the autonomic balance can be shifted either to the sympathetic or the parasympathetic side and that these alterations are associated with characteristic changes in the responsiveness of the autonomic system. It was also mentioned that stimuli acting directly on autonomic central structures change the state of autonomic tuning in the same manner as previously described for reflex stimuli. Thus a state of sympathetic tuning results either from hypotension or from mild stimulation of the posterior (sympathetic) hypothalamus. In either case the central sympathetic discharges are increased: in the former case as the result of a release of autonomic "centers" from the reflex inhibition originating in the carotid sinus, in the latter as the consequence of direct stimulation. In both instances the reactivity of the sympathetic nervous system is enhanced.

These findings have an important bearing on an entirely different problem. If stimuli acting on the sympathetic system are more effective in conditions in which the rate of sympathetic discharges is increased in central autonomic structures, the effectiveness of the stimuli must indicate and be a measure of the excitability of these central structures. In view of the great influence of the hypothalamus on autonomic discharges, its importance for the emotions, and its effect on the functions of the cerebral cortex, the problem of measuring the excitability of the hypothalamus in different states of excitability and autonomic balance was subjected to an experimental analysis.

For this purpose several procedures were used. In one group the excitability of the posterior hypothalamus and its rate of sympathetic discharge were altered by the injection of minute quantities of pentothal or procaine into this structure. Before the injection, and at various intervals of time after it, the hypothalamus was stimulated and the effect of the stimulation on the blood pressure, heart rate, and contraction of the nictitating membrane recorded. Changes in the excitability of the posterior hypothalamus were indicated by corresponding changes in the degree of the sympathetic action on the above-named indicators. The action of hypotensive drugs (mecholyl, acetylcholine, and histamine) was also studied under these conditions because the previously discussed experiments had shown that the drugs elicited a sympathetic effect, indicated by the contraction of the nictitating membrane and the acceleration of the heart rate.*

The intrahypothalamic injection of pentothal or procaine decreased the responsiveness of the posterior hypothalamus to electrical stimulation. At the same time the sympathetic effects produced by the injection of the hypotensive drugs were diminished or abolished. About half an hour after the injection the original effects were restored. From this it follows that the changes in the excitability of the posterior (sympathetic) hypothalamus produced by the intrahypothalamic injection of pentothal or procaine are reflected similarly in the two sets of tests. Consequently, the action of the hypotensive drugs may be taken as a measure of sympathetic hypothalamic excitability.

To study this relation further, a large group of experiments (see Table 1 and Figs. 46, 47) was performed. It was found that not only the heart rate and the contraction of the nictitating membrane underwent characteristic changes after the injection of pentothal into the posterior hypothalamus, but that the hypotensive action of the drug was distinctly prolonged. The return of the blood pressure to the control level was delayed and the hypertensive phase which frequently followed the hypotensive phase under control conditions, particularly in the experiments with histamine, was abolished. The regular occurrence and reversibility of these phenomena prove that, as the sympathetic excitability of the posterior hypothalamus is lessened, the hypotensive action of mecholyl and related drugs becomes prolonged. *The experiments suggest that the size of the hypotensive area is, other conditions being equal, a measure of the sympathetic excitability of the posterior hypothalamus* (see footnote, p. 90).

The experiments were extended to another pair of drugs (metrazol and strychnine). These were likewise injected into the posterior hypothalamus and produced, as expected, an increase in sympathetic responsiveness to direct electrical stimulation. Reflex sympathetic responsiveness (Figs. 43–45 and Table 1) was also greatly increased.

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* The reader will remember that the fall of the sino-aortic pressure was shown to be responsible for these sympathetic effects.

This alteration in sympathetic reactivity appeared, as far as the blood pressure is concerned, in its quicker return from a drug-induced hypotension to the control level and in a greater subsequent hypertensive phase than was seen under control conditions. These effects were likewise reversible.

The excitability of the posterior hypothalamus was altered not only by pharmacological procedures but by physiological techniques. First, advantage was taken of the fact that in very lightly anesthetized animals periods of arousal, characterized by pupillary dilatation, contraction of the nictitating membranes, and spontaneous movements, alternate with periods of sleep. When a hypotensive drug was applied during the arousal period, the return of the blood pressure from the hypotension was faster than during the period of sleep (see Fig. 48). A similar arousal effect was obtained during the inhalation of 5 to 8 per cent carbon dioxide (Fig. 50), which is known to increase the excitability of the hypothalamus and to produce a generalized excitation of the cerebral cortex. Finally, the posterior hypothalamus was stimulated electrically either with suprathreshold stimuli or, as Figure 49 shows, with threshold or subthreshold stimuli which by themselves do not alter the blood pressure. When during the period of stimulation a hypotensive drug was injected, the hypotensive area was considerably smaller than during the control tests. These three groups of experiments show that states of increased excitability of the posterior hypothalamus cause a diminution in the hypotensive action of mecholyl, acetylcholine, or histamine, an effect often followed by a hypertensive phase.

In a final group the excitability of the posterior hypothalamus was lowered by placing lesions in it confined, according to the histological preparations, to this area. Here again (see Figs. 51, 52, and Table 2) it was found that with decreasing excitability of the posterior hypothalamus the return of the blood pressure from the drug-induced hypotension was delayed. *The experiments show that the excitability of the posterior hypothalamus has a decisive and characteristic influence on the action of hypotensive drugs regardless of the procedure used for the alteration of this excitability. If the excitability is increased, the blood pressure returns from the hypotension more rapidly than in the control test, whereas if it is decreased, the return is delayed. Moreover, the tendency toward a hypertensive phase following the drug-induced hypotension, and the magnitude of it, increase with increasing excitability of the posterior hypothalamus.*

Since the relation of the anterior hypothalamus to parasympathetic functions is well established, an attempt was made to investigate the influence of an alteration of the excitability of the anterior hypothalamus on a parasympathetic reflex. The noradrenaline-induced pulse slowing, previously used in our "tuning" experiments, was chosen.

Two groups of experiments were performed. In the first, the excitability of the anterior hypothalamus was lowered by the injection of minute quantities of barbiturates into this structure; in the second, the same effect was accomplished by placing bilateral lesions between the anterior commissure and the optic chiasma. The results of both series (see Figs. 53–56) were the same. The reduction in the excitability of the anterior hypothalamus was accompanied by a reduction in the parasympathetic pulse-slowing reflex. This reduction was reversible in the drug experiments, but irreversible in the coagulation experiments. Since the pulse slowing is a function of the rise of the blood pressure, it is important to emphasize that the lessening of the pulse-slowing reflex after an intrahypothalamic injection or lesion occurred even though the pressor effect of noradrenaline was not lessened by these procedures. As a matter of fact, in some experiments even greater increases in the blood pressure produced by the injection of higher doses of noradrenaline failed to produce a reflex slowing of the degree obtained in the control test at lesser rises of the blood pressure!

Since the reciprocal relations between parasympathetic and sympathetic functions persisted during reflex tuning of the autonomic nervous system (Chapter 2, Section D), the question arose whether such reciprocity remained in conditions of imbalance produced at the hypothalamic level. The experiments proved that this was the case. A state of hypothalamic parasympathetic hyporeactivity induced by the coagulation of the *anterior* hypothalamus was associated with a *greater* reactivity of the *posterior* hypothalamus to electrical stimulation (Fig. 55) and a quicker return of the blood pressure from the drug-induced hypotensive action (Figs. 56, 57). Conversely, it was found that a state of hypothalamic sympathetic hyporeactivity induced by coagulation of the posterior hypothalamus was accompanied by an increased effectiveness of the noradrenaline-induced pulse-slowing reflex (Fig. 58). *It follows from these experiments that parasympathetic hypothalamic hyporeactivity is associated with sympathetic hyperreactivity (indicated by the hypotensive drug test) and that sympathetic hypothalamic hyporeactivity is accompanied by parasympathetic hyperreactivity (indicated by the noradrenaline test).**

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* Concerning the important tonic effects of the hypothalamus on the blood pressure and heart rate and the importance of these findings for the problem of hypertension, see Chapter 2, Sections E and F.

## B. PHYSIOLOGICAL AND CLINICAL INVESTIGATIONS ON THE MECHOLYL AND NORADRENALINE TESTS IN MAN

The most important conclusion from these experiments is this: Drug-induced hypotensive action is an indicator of the sympathetic excitability of the posterior hypothalamus, whereas the noradrenaline pulse-slowing reflex is an indicator of the parasympathetic excitability of the anterior hypothalamus. The latter reflex is immediately applicable to man; concerning the former a decision had to be made which of the hypotensive drugs and which of the sympathetic effects elicited by the hypotension are best suited to clinical purposes.

Since in the animal experiments the changes in the blood pressure were more marked than those in the heart rate (the nictitating membrane is restricted to the cat), the use of the blood pressure suggested itself. It was expected that the size of the hypotensive area was indirectly related to the sympathetic reactivity of the hypothalamus. The size of this area, as was pointed out previously, is determined chiefly by the slope of the blood pressure curve leading from the hypotension to the control level or to the hypertensive phase.

An adequate hypotensive drug must fulfill the following requirements: (a) it must permit an accurate determination of the hypotensive area; (b) the action of the drug on the blood pressure must be reproducible; (c) the drug must be innocuous so that it may be used with a large variety of patients.

Our tests with histamine were unsatisfactory for two reasons: first, a severe headache was frequently produced; second, when the histamine test was repeated after a few days, the hypotensive area was often found to be quite different from that obtained in the first test. Acetylcholine, which was found very suitable for physiological studies in animals, had to be rejected because its effect is too fleeting and would require intra-arterial recording of the blood pressure. Mecholyl, already extensively used by Funkenstein and others (2), fulfilled all three requirements.*

As in Funkenstein's work, the systolic blood pressure was taken at half-minute and one-minute intervals, and the data were graphed. The hypotensive and hypertensive areas were determined with a planimeter. If the hypertensive area was 100 (6.45 cm.$^2$) and more, the patient was said to belong to Group I regardless of the size of the preceding hypotensive area. On the basis of these readings the following classification was made:

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* See also item 313.

| | *Planimeter Reading*[*] | *Area in cm.*$^2$ |
|---|---|---|
| Group I | ....+100 and more | +6.45 |
| Group II | ....−550 to +99 | −35.48 to +6.39 |
| Group III | ....−551 and larger negative values | −35.54 |

The first is thought to be the sympathetically hyperreactive hypothalamic group, the third the hyporeactive. Group II is the intermediate one.

Before an evaluation of the state of the autonomic system under clinical conditions could be made, an adequate series of control tests was needed. Since earlier investigations on rats (269) had suggested that sympathetic reactivity decreases rapidly with increasing age, an attempt was made to cover a large range of ages for both sexes.[†] One hundred and four persons served as experimental subjects. Mecholyl was injected intramuscularly, as in Funkenstein's work (10 mg. per person).

Table 7 shows a fundamental alteration in the response to mecholyl with increasing age. Whereas the intermediate group (II) remained fairly constant, Groups I and III changed markedly and inversely with increasing age. Group I decreased from 31 per cent among the young to 24 per cent among the middle aged and to 5 per cent among the old. Group III, however, increased with increasing age, since no hyporeactors were present in the young group, 2 per cent appeared in the middle, and 28 per cent in the old group. This shift in the distribution of the mecholyl curves with increasing age shows no sex differences. *In the light of the physiological work described in this book, it is concluded that sympathetic central reactivity decreases with increasing age in normal persons.*

This series of experiments was repeated on patients from the psychiatric wards of hospitals and state institutions,[‡] on a total of 236 persons (Table 8). In spite of significant differences between this and the control group, to be discussed presently, the influence of age on the autonomic reactions of patients with neuropsychiatric disorders

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[*] The hypotensive area is indicated negatively, the hypertensive area positively. The area was measured on graphs with time (1 min. = 1 cm.) as abscissa and blood pressure (5 mm. Hg. = 1 cm.) as ordinate.

[†] This work and the subsequently described clinical studies were performed in collaboration with Dr. Ralph Nelson. We are greatly indebted to Mr. Max Williamson of the Mental Health Association and to the *Minneapolis Star Journal* for helping us to secure volunteers for these tests.

[‡] I wish to express my thanks to Dr. Hastings and Dr. Scheele of the University of Minnesota Hospitals, Dr. Anderson of the Minneapolis General Hospital, Dr. Sheiley and Dr. Grimes of the State Hospitals at Hastings and St. Peter. The greater part of this work was carried out at St. Peter, Minnesota.

Table 7. The Influence of Age on the Reactivity of "Normal" Persons to Mecholyl

| Group* | Male | Female | Total | Percentage |
|---|---|---|---|---|
| | | *Age 25 and Under* | | |
| I | 8 | 6 | 14 | 31 |
| II | 12 | 19 | 31 | 69 |
| III | 0 | 0 | 0 | |
| Total | 20 | 25 | 45 | |
| | | *Age 26 to 45* | | |
| I | 3 | 6 | 9 | 24 |
| II | 15 | 13 | 28 | 74 |
| III | 0 | 1 | 1 | 2 |
| Total | 18 | 20 | 38 | |
| | | *Age 46 and Over* | | |
| I | 0 | 1 | 1 | 5 |
| II | 8 | 6 | 14 | 67 |
| III | 0 | 6 | 6 | 28 |
| Total | 8 | 13 | 21 | |

* I, II, and III refer to the sympathetic hyperreactors, the intermediate group, and the sympathetic hyporeactors respectively (see p. 78 for the description of the three types of mecholyl curves).

Table 8. The Influence of Age on the Reactivity of Neuropsychiatric Patients to Mecholyl

| Group* | Male | Female | Total | Percentage |
|---|---|---|---|---|
| | | *Age 25 and Under* | | |
| I | 18 | 2 | 20 | 56 |
| II | 6 | 5 | 11 | 30 |
| III | 3 | 2 | 5 | 14 |
| Total | 27 | 9 | 36 | |
| | | *Age 26 to 45* | | |
| I | 26 | 23 | 49 | 39 |
| II | 33 | 29 | 62 | 49 |
| III | 8 | 7 | 15 | 12 |
| Total | 67 | 59 | 126 | |
| | | *Age 46 and Over* | | |
| I | 3 | 9 | 12 | 17 |
| II | 19 | 8 | 27 | 36 |
| III | 11 | 24 | 35 | 47 |
| Total | 33 | 41 | 74 | |

*Group I includes the sympathetic hyperreactors; Group II is the intermediate group; Group III includes the sympathetic hyporeactors.

was similar to that found in the group of normal people. Here again Group I decreased with increasing age (from 56 per cent to 17 per cent), whereas Group III increased from 14 per cent to 46 per cent. The variations with age which occurred in the intermediate group were somewhat larger than those seen in the control group (Table 7). In each instance the intermediate group was largest for the age group of 26 to 45 years. It is concluded from this work that sympathetic reactivity as measured by the mecholyl test declines in normals and psychotics with increasing age.

A comparison between the data obtained on normals and those obtained on psychiatric patients disclosed marked differences between these two populations in each age group. A considerable majority of normal persons falls at each age into Group II, varying between 67 and 76 per cent, and this is the reason why the degree of sympathetic reactivity indicated by Group II may be considered the standard physiological level. This group was found in the clinical group to be considerably lower (between 30 and 50 per cent). *The hypo- and hyperreactions of the sympathetic system are more numerous in the clinical than in the normal group.* This statement is based on a comparison between similar age groups.

The hyperreactive cases (mecholyl Group I) represent the largest fraction of the abnormal subjects at age 25 and less, whereas the hyporeactive cases (mecholyl Group III) represent the largest fraction of the abnormal subjects at age 46 and more.

The difference between the normal and abnormal groups is, although considerable, in most instances only quantitative, since hyporeactive and hyperreactive individuals are found in both groups. It

Table 9. The Relation between the Diagnosis of Various Neuropsychiatric Disorders and the Groups into Which Patients Fall on the Mecholyl Test

| Diagnosis | Grouping | | | Total No. of Patients |
|---|---|---|---|---|
| | I* | II | III | |
| Schizophrenia | 39 | 55 | 29 | 123 |
| Psychopathic personality | 17 | 14 | 6 | 37 |
| Personality disorders including juvenile delinquency and alcoholism | 7 | 7 | 2 | 16 |
| Psychoneurosis | 6 | 5 | 3 | 14 |
| Manic-depressives | 1 | 0 | 4 | 5 |
| Depression | 0 | 2 | 3 | 5 |
| Other | 10 | 18 | 8 | 36 |
| Total | 80 (34%) | 101 (43%) | 55 (23%) | 236 |

* By contrast, out of a total of 104 normal persons, 23, or 22 per cent, fall into Group I; 74, or 71 per cent, into Group II; 7, or 7 per cent, into Group III.

Table 10. The Influence of Age on the Reactivity of Schizophrenes to Mecholyl

| Group* | Male | Female | Total | Percentage |
|---|---|---|---|---|
| *Age 25 and Under* | | | | |
| I | 5 | 2 | 7 | 54 |
| II | 2 | 0 | 2 | 15 |
| III | 2 | 2 | 4 | 31 |
| Total | 9 | 4 | 13 | |
| *Age 26 to 45* | | | | |
| I | 11 | 14 | 25 | 37 |
| II | 16 | 21 | 37 | 54 |
| III | 1 | 5 | 6 | 9 |
| Total | 28 | 40 | 68 | |
| *Age 46 and Over* | | | | |
| I | 1 | 7 | 8 | 18 |
| II | 12 | 4 | 16 | 37 |
| III | 5 | 14 | 19 | 45 |
| Total | 18 | 25 | 43 | |

* Group I includes the sympathetic hyperreactors; Group II is the intermediate group; Group III includes the sympathetic hyporeactors.

Table 11. The Influence of Age on the Reactivity of Psychopathic Personalities to Mecholyl

| Group* | Male | Female | Total | Percentage |
|---|---|---|---|---|
| *Age 25 and Under* | | | | |
| I | 8 | 0 | 8 | 67 |
| II | 3 | 1 | 4 | 33 |
| III | 0 | 0 | 0 | |
| Total | 11 | 1 | 12 | |
| *Age 26 to 45* | | | | |
| I | 9 | 0 | 9 | 45 |
| II | 7 | 0 | 7 | 35 |
| III | 4 | 0 | 4 | 20 |
| Total | 20 | 0 | 20 | |
| *Age 46 and Over* | | | | |
| I | 0 | 0 | 0 | |
| II | 3 | 0 | 3 | 60 |
| III | 2 | 0 | 2 | 40 |
| Total | 5 | 0 | 5 | |

*Group I includes the sympathetic hyperreactors; Group II is the intermediate group; Group III includes the sympathetic hyporeactors.

should be emphasized, however, that in the young group (age 25 and under) *hyporeactive persons are found only in the abnormal group.* This finding is based on a study of 45 normals and 36 abnormals.

Table 9 shows the distribution of Groups I to III (reactivity to mecholyl) in various neuropsychiatric disorders. There seems to be a greater tendency for the manic-depressive group and those having depressions to consist of sympathetic hyporeactors than for the other clinical groups to do so. However, our numbers are still too small, particularly if the data were to be evaluated separately for various age groups. Such evaluation, however, is possible for the schizophrenic patients and the psychopathic personalities, who comprise 124 and 37 persons respectively. If Tables 10 and 11 are compared with Table 7 (controls), the following facts stand out:

1. Our earlier statement that sympathetic hyporeactors and hyperreactors are more frequent in the abnormal than in the control group holds for the schizophrenic and the psychopathic groups.
2. That hyperreactors decline in number and hyporeactors increase with increasing age holds for these specific groups if the young and old groups are compared. Group III is, however, not larger in the middle-aged group than in the young group of schizophrenes.
3. The psychopathic group is closer to the controls than the schizophrenic group. The psychopaths show at age 25 years and less considerably more hyperreactors than the controls, but they share with them the absence of hyporeactors.

Thus, by comparing the "abnormals" with a group of "normals" of similar age, significant differences in the reactivity to mecholyl between the two groups have been established. In the light of our experimental work these findings indicate that sympathetic central reactivity, presumably at the hypothalamic level, shows gross deviations in a large percentage of neuropsychiatric cases. There seems to be a tendency for psychopaths to be sympathetic hyperreactors, whereas among schizophrenes both hyporeactors and hyperreactors are found at a young age. Before a further evaluation of these findings is attempted, the important question must be decided whether or not these autonomic deviations are significantly related to the disease process.

Funkenstein *et al.* (79) were the first to apply the mecholyl test in a large number of patients with neuropsychiatric disorders. Since the significance of the age factor was not known at that time, the comparison between the reactions found in their clinical and control groups loses a great deal of its validity, but their important studies on the behavior of normal and psychotic persons in different emotional states and before and after certain types of treatment are of great interest. On student volunteers it was observed that the mecholyl curve was significantly altered in conditions of emotional stress. Moreover, depending on the type of emotional behavior, different types of mecholyl reactions were observed. This finding will be discussed later in its specific relation to the theory of the emotion. In view of the large body of facts showing the key role of the hypothalamus in the emotions it suffices, at present, to point out that these data strongly support the assumption that the mecholyl curve is determined in man by the excitability of the hypothalamus, in agreement with our experimental work on the cat. This interpretation of Funkenstein's work is applicable to his studies on psychiatric patients. The patients who spontaneously or under the influence of treatment showed a marked change in behavior reacted differently to mecholyl before and after the treatment. The authors further state that "when the psychological picture changes, the physiological picture changes and vice versa." Apparently, improvement or impairment of the clinical condition of the patient was associated with an alteration in the blood pressure reaction induced by mecholyl. If this reaction did not change, the clinical picture was unaltered. Moreover the changes in the autonomic reactions were associated with clinical improvement regardless of the means through which the clinical (psychological) changes in the patient's condition were brought about.

It may therefore be said that the emotional states induced experimentally in normal persons and the psychological changes occurring spontaneously or resulting from the application of therapeutic procedures in psychiatric patients lead to characteristic changes in the mecholyl curve, indicating a change in sympathetic excitability, presumably at the hypothalamic level. Consequently, if the mecholyl curve of Type III (marked and prolonged hypotensive action) is changed into one of Type II (intermediate size of the hypotensive area) or even into Type I (small hypotensive area with distinct hypertensive phase), this change signifies an increased excitability of the sympathetic division of the hypothalamus regardless of whether the change occurred spontaneously or was the result of medical treatment. A corresponding interpretation is to be given to changes occurring in the opposite direction. The practical implications of this interpretation will be discussed later.

In order to complete the study of the autonomic reactivity of the hypothalamus in man, an investigation was carried out on the effect of noradrenaline on the blood pressure and heart rate of normal persons and neuropsychiatric patients. Noradrenaline in the amount of 0.005 mg. was injected intravenously, and the blood pressure and heart rate were determined first at half-minute and later at one-minute intervals. The quotient

$$\frac{\text{Maximal rise in the systolic blood pressure}}{\text{Maximal diminution in the heart rate}}$$

served as a measure of the parasympathetic excitability of the hypothalamus.*

In spite of the simplicity of this index the results were found to be complex. Even in the control group the P.I.† showed very wide variations regardless of whether the changes in the blood pressure and heart rate were taken as absolute differences or as percentage changes. Nevertheless, some results were quite clear. We determined the percentage of cases with a P.I. of 0–1.0, 1.1–2.0, 2.1–3.0, etc., and found that with increasing age there is a clear shift toward the higher P.I.'s, as indicated in Table 12. Such a shift was seen likewise if the P.I. was calculated on the basis of the percentage changes in the blood pressure and heart rate. It follows that parasympathetic reflex excitability decreases with increasing age.

Experiments on the neuropsychiatric group were performed in a similar manner. Here again the percentage of cases with a high P.I. increased with increasing age, and this result, in agreement with the work on normal persons, was derived from absolute as well as percentage changes in the blood pressure and heart rate. The psychiatric group as a whole showed less change with age than the normal group (Table 12).

The P.I. was studied also in the normal and psychiatric groups in its relation to the initial pulse rate. It was to be expected that, other conditions being equal, the faster the initial pulse rate, the greater the slowing of the heart rate in response to the noradrenaline-induced rise of the blood pressure. In the normal group this was the result obtained (Table 13) regardless of whether the P.I.'s were based on absolute or percentage values. In the psychiatric group, however, this dependence of the P.I. on the initial heart rate was absent. The data suggest that the reactivity of the parasympathetic system (presumably at the hypothalamic level) as measured by the relation of the P.I. to age and initial pulse rate is less in the psychiatric than in the con-

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* Barucci (12) carried out some work on the changes in the heart rate of psychiatric patients in which he used 100 times as much noradrenaline (0.5 mg.). He reported his results by adding the increase of the systolic blood pressure and the decrease of the heart rate. It is obvious that the data thus obtained bear no relation to the reactivity of the parasympathetic system.

† Parasympathetic index. The smaller the P.I., the greater the excitability of the parasympathetic system.

Table 12. The Influence of Age on the Parasympathetic Index (P.I.)*

| Age | Percentage of Persons with a P.I. of | |
|---|---|---|
| | 3–4 | 5 and more |
| *Normal Persons* | | |
| 30 years and less | 23.5 | 5 |
| 31–45 years | 28.5 | 13.5 |
| 46 years and more | 72.0 | 49 |
| *Psychiatric Patients* | | |
| 30 years and less | 35 | 15 |
| 31–45 years | 43 | 17.5 |
| 46 years and more | 64 | 33 |

* Based on $\frac{\text{Change in blood pressure in mm.}}{\text{Decrease in heart rate}}$

The quotient is determined on the basis of the maximal changes in blood pressure and heart rate following the intravenous injection of 0.005 mg. of noradrenaline.

Table 13. The Influence of the Initial Pulse Rate on the Parasympathetic Index * of Persons 30 Years Old and Younger

| Initial Pulse Rate | Percentage of Persons with a P.I. of 0–1 | |
|---|---|---|
| | Normals | Psychiatric Patients |
| 40–59 | 8 | 43 |
| 60–69 | 33 | 46 |
| 70–79 | 40 | 54 |
| 80 and over | 81 | 31 |

* The P.I. was obtained from calculating the percentage changes in the blood pressure and heart rate.

trol group. They seem to indicate also that the central tone of the parasympathetic system does not determine the excitability of a parasympathetic reflex in the psychiatric group.

An attempt was made to correlate the P.I. with the sympathetic reactivity established by the mecholyl test. No significant correlation was found, however, since a wide range of P.I.'s was observed in all three types of the mecholyl curve.*

Obviously a great many problems remain to be solved before the parasympathetic and sympathetic functions and their interrelation can be determined accurately. But a beginning has been made. The recognition of the mecholyl test as a measure of sympathetic hypothalamic reactivity should become a valuable tool for psychiatric research and therapy.

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*Since this was written Dr. R. Nelson studied our clinical materials statistically and was able to show that cases of autonomic imbalance in which strong sympathetic reactivity was associated with weak parasympathetic reactivity and vice versa were more common in the neuropsychiatric patients than in the control group. The effect of age and the differences between the control and the psychiatric groups were found to be highly significant statistically ($p = <0.001$ or between 0.01 and 0.001) in the different groups of experiments.

More attempts should be made to determine the differences in parasympathetic reactivity between normal persons and mental patients. Our studies have shown that sympathetic and parasympathetic reflexes heretofore considered to be medullary depend in their quantitative aspects on the hypothalamus. The hypothalamus need not be present for these reflexes, but if present, as in the normal organism, its excitability determines the threshold of these reflexes. Two well-known principles underlie this phenomenon. One, that several levels of the neuraxis are involved in the same or closely related functions (see Barcroft's principle of duplication, 8). The other, that at these levels the sensitivity to various stimuli and the metabolic activity are closely related, and decrease in the following order: cortex, hypothalamus, medulla oblongata (168). If this is the case, numerous other parasympathetic reflexes should be investigated in their relation to the hypothalamus in the experimental animal, and the results applied clinically in an attempt, paralleling the mecholyl test and its significance for the evaluation of the sympathetic system, to reveal significant parasympathetic differences between normal people and mental cases. The heart-slowing reflex following a pressure on the eyeball (132) and an observation made by Barucci should be studied further. This author found that the pressor effect of noradrenaline, administered in large doses intramuscularly, was greatest in patients having depressions, lowest in hebephrenic and catatonic cases, and intermediate in epileptics. The pulse slowing declined in the same order. Consequently no evidence for a difference in the pulse-slowing parasympathetic reflex was shown. Barucci misinterprets his data by neglecting the elementary fact that the pulse slowing is directly related to the rise of the blood pressure. How the marked differences in the pressor response are to be interpreted is not certain. If it may be assumed that the response of the peripheral structures (heart, blood vessels) is rather constant, the different pressor effects might be due to differences in the sensitivity of the parasympathetic baroreceptor reflexes which tend to restore the normal blood pressure. This possibility should be investigated.

CHAPTER 11

# THE HYPOTHALAMIC-CORTICAL SYSTEM IN HYPOTHALAMIC IMBALANCE. REVIEW AND CLINICAL APPLICATION

THE investigations discussed thus far have been concerned with the measurement of autonomic reactivity in states of autonomic and, specifically, of hypothalamic imbalance and with the influence of this imbalance on the sympathetic and parasympathetic "downward" discharge. The last decade has shown that, in addition, the hypothalamus exerts a profound influence on the cerebral cortex as a whole. We have to sketch, therefore, the nature and significance of this "upward" discharge, both in general and in conditions of altered hypothalamic excitability in particular.

If the posterior hypothalamus is stimulated electrically, a rage reaction is elicited which is characterized not only by well-known autonomic symptoms but also a specifically directed attack (Hess). Such direction is missing if the stimulation is performed in the decorticate animal. Observations of this kind suggested that under conditions of emotional excitement or direct stimulation of the posterior hypothalamus, the cerebral cortex would be influenced. On this basis Cannon postulated an upward discharge from the diencephalon in emotion, and Papez (249), in an ingenious paper, implemented the concept. Direct evidence for a hypothalamic-cortical discharge was obtained by studying cortical action potentials under conditions of stimulation of the posterior hypothalamus (242). Cortical potentials recorded in the normal and convulsive states (the latter induced by the topical application of strychnine) showed clear signs of excitation (asynchrony of normal potentials and increased frequency of strychnine spikes), and this effect appeared in both cerebral cortices.

Other, and perhaps more physiological, forms of excitation of the posterior hypothalamus caused similar upward discharges. Thus nociceptive (101) or proprioceptive stimuli (21) induced an excitation of the hypothalamus and the cerebral grey matter, and the inhalation carbon dioxide (Fig. 80) produced similar effects.

The functional significance of these diffuse discharges lies in their relation to the phenomenon of awareness. It is well known that stimuli excite specific sensory projection areas of the cortex even in the deeply anesthetized organism. On the other hand, states of attention produce diffuse changes in the potentials of the EEG. Apparently the cortex receives impulses via the specific projection systems which lead to an excitation of restricted areas of the cortex (the auditory area, for instance). In addition, as Magoun and his group have shown, there exists a diffuse multisynaptic system which sends impulses from the reticular formation of the brain stem to the posterior hypothalamus and from both structures to the cortex via the diffuse projection system of the thalamus. Lesions in this system lead to coma, and the corticogram shows large, slow, delta potentials. On the other hand, sectioning the specific afferent systems in the brain stem does not alter the cortical potentials, and the posture remains normal. Sleep occurs spontaneously, and arousal can be induced by appropriate stimuli.

That the diffuse afferent system contributes to awareness is evident from the following observations on very lightly anesthetized animals. If these animals were aroused and such an arousal was evident from movements, pupillary dilation, contraction of the nictitating membrane, etc., the cortical excitation was diffuse and associated with an excitation of the hypothalamus. Moreover, the hypothalamic-cortical discharge was reduced ipsilaterally after a unilateral lesion in the posterior hypothalamus (201). On the other hand, if the stimulus caused no arousal reaction, neither excitation of the hypothalamus nor diffuse excitation of the cortex occurred (Fig. 81).

Systematic experiments showed the interaction of the two afferent systems. On the basis of action potential studies, it was found that the responsiveness of a cortical area to its specific afferent system was increased by simultaneous stimulation of the diffuse system, either directly in the hypothalamus or reflexly by, for instance, nociceptive stimuli. The increased reactivity that was present even when the hypothalamus or the nociceptive nerves were stimulated with near-threshold currents seems to account for the quantitative and possibly qualitative alterations in the sensations and perceptions in states of emotion: If an awake but rather drowsy cat was exposed to slight acoustic stimuli, it did not respond, but in the presence of slight stimulation of the posterior hypothalamus these stimuli evoked distinct responses, such as turning of the head toward the side of stimulation.*

Alterations in hypothalamic balance induced by the injection of metrazol or pentothal led to corresponding changes in the hypothalamic-cortical discharge. The latter was found to parallel the excitability of the posterior hypothalamus and the sympathetic downward discharge. If we bear in mind that the interaction of the hypothalamic-cortical discharge with the discharges of the specific afferent systems (auditory, visual, etc.) represents one of the conditions of perception (97, 122, 123), it is understandable that any alteration in hypothalamic balance may lead to changes in these fundamental elements of behavior (237) and thereby to profound disturbances of the personality.

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* It could be shown that the responsiveness of the motor cortex was likewise increased upon hypothalamic stimulation (Chapter 7). The improvement in affective states of motor functions of apractic patients (35) is probably related to the enhanced hypothalamic-cortical discharge under these conditions.

The parallelism between the hypothalamic upward discharge and the sympathetic downward discharge is important for an understanding of certain empirical data concerning the mecholyl test. Funkenstein noted that changes in the blood-pressure reaction to mecholyl were associated with changes in the psychological behavior of the patient. In order to understand this relation, it should be borne in mind that changes in the response to mecholyl are due to alterations in the excitability of the hypothalamus. Moreover, it could be shown that the fall of the blood pressure induced by mecholyl leads to an excitation of the posterior hypothalamus (Fig. 87). This excitation leads to a downward discharge, the intensity of which is related to the excitability of the hypothalamus, and also to an upward discharge (Figs. 89, 90) paralleling the intensity of the downward discharge. Therefore, a change in the mecholyl test reflects also a change in the hypothalamic-cortical discharge which, as was pointed out earlier, is intimately related to perception and behavior.

Shagass's work (277, 279) on the sedation threshold seems to be related to the intensity of the hypothalamic-cortical discharge. He found that the amount of sodium amytal necessary to produce a certain change in the EEG was greater during states of tension and anxiety than in the relaxed state and provided a measure of the degree of tension in various clinical conditions. As was mentioned earlier, barbiturates act specifically on the multisynaptic reticulo-hypothalamic-cortical system, and the mecholyl test discloses, in states of tension, an increased sympathetic hypothalamic excitability, which is associated with increased hypothalamic-cortical discharges.

Greenblatt (136) reports that frontal lobotomy is effective in 84 per cent of patients with marked tension, but in practically none with minimal tension. This observation suggests that lobotomy acts chiefly by eliminating the effects on the frontal lobes of an excessive hypothalamic-cortical discharge.

Finally, it should be mentioned that recent experimental work* has shown that the hypothalamic-cortical relation is still more complex. The cortex is not only subjected to hypothalamic impulses but, in turn, gives rise to corticofugal impulses which are of great importance for the excitability of the hypothalamus and thereby for the upward and downward hypothalamic discharges. Since there is a positive feedback relation between the cerebral cortex and the posterior hypothalamus, any change in the excitability of the former is bound to result in a similar change in the excitability of the latter (and vice versa).* Consequently the alterations in hypothalamic-cortical relations become very marked in conditions of hypothalamic imbalance. These experimental findings should be regarded as physiological models of the important interactions which take place between the cortex and the hypothalamus in physiological and pathological conditions. The data indicate that cortical processes are altered as the excitability of the posterior hypothalamus varies in different degrees of wakefulness and in various emotional states. In addition, the work suggests, at least in principle, the mechanism whereby alterations in hypothalamic functions and changes in emotional reactivity may be caused by cortical processes.† The restitution of the emotional balance through psychotherapy is probably accomplished via cortico-hypothalamic pathways. The partial and apparently rather subtle action of drugs such as chlorpromazine on the cortex (Chapter 8) might also result in a change in hypothalamic reactivity through a rather selective and specific diminution of the cortico-hypothalamic discharge.

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* See Chapter 7, Section F.

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* The homeostatic problem involved in this statement is discussed in Chapter 13.

† As, for instance, in a psychiatric interview which results in specific autonomic discharges.

## CHAPTER 12

# THE PHYSIOLOGY OF FEAR AND ANGER

## A. FUNKENSTEIN'S WORK

FUNKENSTEIN (78) published a challenging paper entitled "The Physiology of Fear and Anger" in the *Scientific American*. Although he had originally divided the reactions of his patients to mecholyl into seven groups, he confines himself in this paper to two groups only—according to our investigations distinguishable as sympathetic hyporeactors and hyperreactors respectively. Psychologically the hyporeactors were frightened and depressed, whereas the hyperreactors were "angry at other people." Funkenstein performed the mecholyl test also on students under conditions of emotional stress. In agreement with his observations on psychotic patients, he found that the hyporeactors felt depressed and were anxious or "angry at themselves," whereas the hyperreactors were "angry at others." On retesting the students in a relaxed state, no differences between the two groups appeared. Under ordinary conditions the students were apparently intermediate reactors (our Type II), which the majority of normal persons are.

These findings suggested to Funkenstein that in different states of emotion different types of adrenomedullary secretion take place. He hypothesized that the secretion consists of noradrenaline in the hyperreactors and of adrenaline in the hyporeactors, and supported this thesis by three groups of experiments. In the first group he showed that the blood pressure reaction to mecholyl was characteristically altered by the injection of these neurohumors. Mecholyl elicited the blood pressure curve seen in hyperreactors if its administration had been preceded by an injection of noradrenaline, whereas it elicited the response characteristic for hyporeactors if an injection of adrenaline had preceded. In the second group of experiments, a continuous infusion of noradrenaline or adrenaline was made which elevated the blood pressure. During this hypertensive phase mecholyl was injected. When noradrenaline had been infused, the blood pressure was lowered only briefly by the mecholyl injection and then returned to the hypertensive level, but when adrenaline had been infused, a distinctly greater and more prolonged depression of the blood pressure occurred.

In a third group of experiments, summarized without detailed data, "stressful situations" arousing anger or fear in different persons or in the same person on different occasions led in the angry person to circulatory reactions similar to those produced by the injection of noradrenaline, whereas in the fearful person the circulatory changes indicated the liberation of adrenaline.

On the basis of these data Funkenstein assumed that rage and fear lead respectively to the liberation of noradrenaline and adrenaline. According to the experiments of Holtz *et al.* (173), von Euler and Folkow (297), and others the excitation of the adrenal medulla leads to secretions of noradrenaline and adrenaline in varying proportions in different types of reflexes, although the experimental results were quite variable. Similar results were obtained by Folkow and von Euler (70) on the stimulation of various points in the hypothalamus. Our own work on hypothalamic stimulation and asphyxia (259) showed by the bioassay of noradrenaline and adrenaline that, in general, asphyxia causes adrenaline to appear in the blood whereas stimulation of the hypothalamus leads chiefly to the secretion of noradrenaline. However, occasionally adrenaline was secreted upon hypothalamic stimulation.

## B. PHYSIOLOGICAL CONSIDERATIONS

It behooves us now to correlate the important results of Funkenstein's investigations with the work reported in this book and with other physiological data.

Granted the possibility that stimulation of two discrete points in different parts of the hypothalamus may result in the liberation of noradrenaline and adrenaline respectively, it appears doubtful that a slight difference in the site of hypothalamic excitation should cause rage in one case and fear in the other. The fact that emotional processes are associated with parasympathetic and sympathetic discharges (see items 86 and 94 for the literature), although the parasympathetic symptoms are often obscured by the sympathetic dominance, suggests that the anterior and the posterior hypothalamus are involved and argues against pin-pointing the site of excitation in the hypothalamus under these conditions. An interesting clinical observation supports this idea: very different types of emotions (pleasurable excitement, depression, anxiety, etc.) were found to precipitate an attack of asthma (263), the attack apparently being due to the increase in parasympathetic discharges associated with emotional tension.

Hess (153) reports that on stimulation of the hypothalamus in unanesthetized animals a change from rage to fearlike reactions occurred.

Since the site of stimulation remained the same, I should like to suggest that *a change in the responsiveness of the excited neurons* was involved. It was shown earlier* that aggressive and ragelike actions occurring either upon stimulation of the hypothalamus or upon confronting the cat with a dog, had a tendency to be converted into withdrawal reactions and flight after a curare-like drug (anectin, intocostrin) had been injected in a nonparalyzing dose. Since these drugs reduce the excitability of the posterior hypothalamus (Fig. 72), it is suggested that *the degree of hypothalamic excitation may have a decisive influence on the type of emotion which may be evoked in a given situation, and that the emotion of rage and the state of aggressiveness are associated with a greater hypothalamic excitation than the state of fear.*

Funkenstein seems to assume that in anger and fear noradrenaline and adrenaline are secreted by the adrenal medulla and that this secretion determines the reaction of the blood pressure to mecholyl. He overlooks two facts: (a) That hypothalamic excitation and emotional excitement produce sympathetic effects and lead thereby to the liberation of noradrenaline from sympathetic nerve endings,† as animal studies (46, 257, 296) and observations on the urinary excretion of noradrenaline in man under conditions of increased sympathetic discharges (exercise, hypertension) show (173, 299, 302). (b) That central or reflex excitation of the sympathetic system elicits first a discharge confined to the sympathetic nerves (for brevity's sake called "neurogenic") and later, i.e., with increasing duration and/or intensity of excitation, an additional "hormonal" discharge through adrenomedullary secretion (see Figs. 63 and 68).

Should we assume that only the adrenomedullary secretion, but not the neurogenic discharge, is of importance for the action of mecholyl? This would be contrary to the results of our experimental work (Fig. 49) in which hypothalamic excitation even with threshold stimuli was found to decrease the hypotensive area produced by mecholyl. Similar results were obtained when mecholyl was applied during a sympathetico-adrenal discharge produced by strong hypothalamic stimulation or by asphyxia, although the adrenomedullary component consists chiefly of noradrenaline in the first case, and of adrenaline in the second case. These and other experiments (see also Fig. 42) show that if "neurogenic" and adrenomedullary discharges ‡ are combined as they are under conditions of strong central excitation, the action of mecholyl is determined by the intensity of the neurogenic discharge. If, on the other hand, noradrenaline or adrenaline is injected intravenously in small quantities which raise the blood pressure temporarily, a state of parasympathetic "tuning" prevails and, in accordance with the rules of autonomic tuning discussed previously, the hypotensive action of mecholyl is aggravated (Fig. 71).

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* See Chapter 4.

† And possibly from adrenomedullary secretion.

‡ The normal and denervated nictitating membranes serve as indicators of the "neurogenic" and adrenomedullary discharges respectively.

These data do not support Funkenstein's interpretation of the physiology of anger and fear and its relation to specific adrenomedullary secretions. His work, however, has been confirmed in essential features by others, as we shall see presently. It is therefore important to attempt to reconcile, if possible, these conflicting experimental and clinical data, which have been obtained by quite different technical approaches and points of view.

It was mentioned earlier that upon hypothalamic stimulation of the awake cat a change from aggressiveness to withdrawal, suggesting a change in the emotional state from rage to fear, may occur spontaneously or as the result of subparalytic doses of curare-like substances. Both observations are compatible with the assumption that different intensities of hypothalamic excitation are involved in the two forms of emotion. As the stimulation goes on, the reactivity of the hypothalamus is likely to be lessened and then fear reactions appear (Hess). Similarly, when the proprioceptive discharges, the great importance of which for the excitability of the posterior hypothalamus has been stressed, are diminished by curare-like substances, there is a similar change from aggression to withdrawal. Wolff (322a) emphasizes the fact that muscular contractions are quite common in states of anger and resentment in man. They are not confined to the mimic muscles of the face, but occur frequently in the temporal muscle (247) and in the striated muscles of the legs and back. The sustained character of these contractions may lead to pain in these areas.

In fear, terror, and similar states it is generally assumed that the tone of the skeletal muscles is low. Consequently it is likely that in anger the neurogenic discharge—and with it, the liberation and excretion of noradrenaline—is high, but low in fear and anxiety. The intensive neurogenic sympathetic discharge in anger, whether it is combined with a secretion of noradrenaline from the adrenal medulla or not, accounts for the lesser hypotensive effect of mecholyl and for the greater excretion of noradrenaline—to be discussed presently—in this condition.

A great difficulty, however, is how to account for the greater hypotensive effect of mecholyl in fear in spite of a considerable sympathetico-adrenal discharge which leads to the liberation of significant amounts of adrenaline from the adrenal medulla. If it were possible to show that under certain conditions a strong adrenomedullary secretion could occur without an intensive neurogenic discharge, and if these conditions were applicable to the state of fear, our problem would be solved, at least in principle.

It was shown earlier that there is a certain antagonism between the adrenomedullary secretion and the neurogenic discharges. If the adrenomedullary secretion is large, it tends to reduce the neurogenic discharge. This antagonism is apparent from the following observations: (a) A strong sympathetico-adrenal discharge, evoked directly (from the hypothalamus) or reflexly, caused first a maximal neurogenic discharge (normal pupil dilated and nictitating membrane contracted; no change in denervated pupil and nictitating membrane). Later an adrenomedullary discharge occurred, leading to maximal changes in the *denervated* ocular structures. *During this phase the neurogenic effects were lessened or disappeared* (see Fig. 68). (b) A strong adrenomedullary secretion occurred on readmission of air following a prolonged asphyxia. If during this phase the hypothalamus was stimulated directly, the sympathetic responsiveness was less than under control conditions (see Fig. 69). The mecholyl test showed under these conditions a more prolonged hypotensive action. *It may be inferred that the reactivity of the hypothalamus to direct and reflex excitation is lessened when the adrenomedullary secretion is considerable.*

Before we consider further studies on the effect of anger and fear on the excretion of neurohumors and associated phenomena, it is well to review the factors which predispose to a large adrenomedullary secretion accompanied by a minimal neurogenic sympathetic discharge.*

The first pertinent observations were made on the influence of nociceptive stimuli on the sympathetico-adrenal discharge in the states of wakefulness and anesthesia. One normal pupil and nictitating membrane served as indicators of the neurogenic discharge, whereas the chronically denervated pupil and nictitating membrane of the other side indicated the adrenomedullary discharge (126).

The quotient *Neurogenic discharge/Adrenomedullary discharge* is referred to as N/A. In the awake cat this quotient is very large or infinite, since the neurogenic effect may be maximal but no hormonal effect may appear on the denervated side. In anesthesia the quotient is very small, since the neurogenic response is minimal but the denervated structures indicate a large hormonal factor. In another group of experiments, asphyxia was chosen as a test stimulus and applied before and after the administration of an anesthetic. In these experiments it was found likewise that the N/A quotient decreased with the increasing depth of the anesthesia.

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* See Chapter 3.

These observations suggested that conditions leading to a diminution of the excitability of the central nervous system, particularly at the cortical and hypothalamic level, would greatly influence the N/A quotient in response to reflex or hypothalamic stimulation. This was indeed the case in experiments in which the N/A quotient was studied in relation to the excitability of the posterior hypothalamus. Thus, if during the course of several hours of experimentation the hypothalamic excitability declined, the N/A quotient in response to a test stimulus (sciatic nerve stimulation or asphyxia) was greatly reduced.

A direct alteration of hypothalamic excitability by the injection of pentothal or metrazol into the posterior hypothalamus altered in opposite manners the sympathetic response to a test stimulus in terms of the N/A quotient. When the excitability was raised by the injection of metrazol, the neurogenic component was distinctly increased, whereas it was diminished upon the intrahypothalamic injection of pentothal. If in the latter experiment an attempt was made to match the effect of the test stimulus with that seen before the injection of pentothal by increasing the intensity of stimulation, the marked decrease of the N/A quotient became apparent. Finally, and most importantly for the interpretation of the types of sympathetico-adrenal discharges occurring in different emotions, it was found that a reduction in hypothalamic excitability through curare-like substances was accompanied by a decrease of the N/A quotient.

From the physiological point of view one of the essential differences between a state of anger and resentment and a state of fear and anxiety is that in the former the excitability of the posterior hypothalamus is at a high level because of the increased proprioceptive impulses originating in the sustained contractions of the skeletal muscles whereas in the latter it is relatively low because of the loss of tone of these muscles.* Since it has been shown that the N/A quotient in response to a strong stimulus declines with decreasing excitability of the hypothalamus, and since the neurogenic discharge is the chief source of noradrenaline and the adrenal medulla the main origin of adrenaline in the blood, one should find in different states of central excitability corresponding changes in the N/A quotient. In anger, therefore, the concentration of noradrenaline should be high in the blood and urine, whereas in fear or anxiety the adrenaline excretion should be increased.

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* On the relation of the gyrus cinguli to fear and terror see item 94, pp. 344–345.

## C. FURTHER STUDIES ON HUMAN EMOTIONS

Concerning the urinary excretion we have data from two different laboratories ( 45, 62, 63, 282, 329). It was found that under conditions of stress, induced by work on Hoagland's pursuit-meter, the excretion of noradrenaline and adrenaline was increased, whereas when the test was performed during the inhalation of 10 per cent oxygen only the excretion of adrenaline was increased. This observation suggests a decrease in the N/A quotient in anoxia.*

Elmadjian and his associates performed some experiments on the effects of mecholyl and insulin hypoglycemia on the excretion of the two neurohumors. The reader will remember that mecholyl leads to an excitation of the posterior hypothalamus and to increased hypothalamic-cortical discharges,† whereas in hypoglycemia the cortex and, eventually, the hypothalamus become depressed (168). Since mecholyl as well as insulin hypoglycemia calls forth a sympathetic discharge, the essential difference between the two procedures is that the excitability of the hypothalamic-cortical system is high in the mecholyl, but low in the insulin, tests. One would, therefore, expect the excretion of noradrenaline to be greater in the mecholyl than in the insulin test and the reverse to be true for the adrenaline excretion. The results, although obtained on a very small number of subjects, seem to bear out this relation. ‡

More extensive and convincing is the work of Silverman *et al.* They determined the blackout level on the human centrifuge (expressed in *g*) in different persons and found that high *g*-tolerance is associated with a high level of noradrenaline excretion. The *g*-tolerance is known to depend on the intensity of the sympathetic discharge, which tends to counteract the accumulation of blood in the abdomen. It seems, therefore, to follow that the reactivity of the sympathetic system in different persons, the *g*-tolerance, and the magnitude of the noradrenaline excretion undergo parallel changes. Pursuing Funkenstein's original observations, the authors noted that the emotional state had a profound influence on the *g*-tolerance. In a state of anger ("after they had expressed some anger or were relatively free from anxiety") two persons showed a high blackout-level, whereas their *g*-tolerance was low when they were "worried, depressed, or anxious." This relation appeared also in different emotional states that had been induced experimentally. When the subjects were grouped according to their emotional states on a scale starting with marked anxiety and ending with a high degree of anger and aggressiveness, the sequence thus obtained corresponded to an increasing degree of *g*-tolerance.

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* The enormous increase in the adrenaline content in severe hemorrhage (311) is another example of this type of sympathetico-adrenal discharge under conditions of a decreased cerebral excitability.

† See Chapter 7, Section E.

‡ Dunér's important investigations showed that the adrenomedullary secretion in hypoglycemia consisted almost exclusively of adrenaline. No change in the adrenaline content of the blood occurred after the nervous discharges on the adrenal medulla had been eliminated through denervation of the adrenals (60). Moreover the excretion of adrenaline is increased in insulin hypoglycemia, whereas that of noradrenaline is unchanged (301).

## D. CONCLUDING REMARKS

Although more work on the excretion of the neurohumors and possibly on their concentration in the blood in different emotional states is needed, the data discussed in this section seem to justify the following conclusions:

1. Hypothalamic excitability is greater in anger and resentment than in states of fear and anxiety. An important factor accounting for this difference is the proprioceptive discharge in anger, originating in the sustained contractions of the striated muscles.
2. The degree of hypothalamic excitability determines the ratio *Neurogenic discharge/Adrenomedullary discharge* and thereby the rates of excretion of noradrenaline and adrenaline. For this reason anger is associated with a high level of noradrenaline excretion and anxiety with a high level of adrenaline excretion.
3. A parallelism exists between the degree of hypothalamic excitability, the rate of excretion of noradrenaline, and the type of the blood pressure curve induced by mecholyl. Consequently either of the two procedures can be used as an indicator of the hypothalamic sympathetic excitability in the intact organism, but the mecholyl blood pressure test is preferable because of its suitability for mass investigations.*

It need hardly be said that a good many questions require further experimental clarification. I do not see how the data discussed in this chapter can be reconciled with the work of Weil-Malherbe (314) on the adrenaline plasma level in different states of consciousness and in mental patients. Moreover, there are certain disagreements which may be due to the fact that the terms "anxiety" and "fear" are used differently by different authors. This might explain why Hinkle and Wolff (169) find in states of fear and anger adrenaline-like pressor reactions, whereas Funkenstein reports that the vascular changes in anger are noradrenaline-like and those seen in fear suggest the presence of adrenaline.*

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* In 1953 (94) I showed that the excitability of the hypothalamus can be measured by the mecholyl test, and have since published, in collaboration with E. S. Redgate, a series of papers (125, 127, 260–262) describing the experiments on which this statement was based. Elmadjian *et al.* write in 1956, without giving credit to our work: "It is thus proposed that by means of methocholine administration, the excitability of these centers may be tested by the measurement of the catechol amines excreted in the urine."

The emphasis in this discussion has been put on the types of sympathetic downward discharges occuring in different emotions because of our interest in obtaining quantitative indicators of central autonomic processes. When it is suggested that the tone of the skeletal muscles has, through proprioceptive impulses, a considerable influence on the kind of emotion observed, it is not intended to support the James-Lange theory. It is rather suggested that the state of the skeletal muscles in rage and fear is part of the emotional process.†

* Graham (134) finds similar vascular reactions in the skin in patients with hostility and anxiety! And Hickam *et al.* (166) believe that some persons show adrenaline-like and others noradrenaline-like vascular changes in anxiety (see also items 1, 225, 226).

† See my discussion of the relation of the gyrus cinguli to muscle tone and fear (94, p. 344).

CHAPTER 13

# THE ROLE OF THE HYPOTHALAMUS IN HOMEOSTASIS

IT IS one of Cannon's great merits to have reintroduced and elaborated Bernard's concept of the constancy of the internal milieu and to have shown the fundamental importance of the autonomic nervous system in homeostasis (38). The new data on autonomic functions presented in this book made it necessary to reconsider the role of homeostasis in physiological and pathological conditions and to apply this concept specifically to the state of autonomic imbalance of the hypothalamus.

## A. NORADRENALINE AND ADRENALINE IN HOMEOSTASIS

It was shown earlier that the rise of the blood pressure resulting from an injection of adrenaline or noradrenaline led to a reduction in the size of the pupil, a relaxation of the normal nictitating membrane (110), and a lessened responsiveness of the sympathetic division of the posterior hypothalamus to electrical stimulation. The secretion of these neurohumors in the postaspyhxial state led to similar results (Fig. 69). It was noted further that during the pressor phase induced by the injection of noradrenaline or adrenaline and during a hypothalamically or reflexly induced rise of the blood pressure, the sympathetic responsiveness of the hypothalamus was reduced and that this effect was abolished by sino-aortic denervation (Figs. 23, 24). The recording and frequency analysis of the action potentials revealed a lessening of the state of excitation of the hypothalamus and the cerebral cortex under these conditions. These changes failed to occur after sino-aortic denervation (Figs. 94, 95). Consequently the diminution in hypothalamic sympathetic reactivity and the lessening of the hypothalamic-cortical discharges seem to be due to sino-aortic baroreceptor reflexes. On the other hand, the fall of the blood pressure through hypotensive drugs led to an excitation of the hypothalamus and, through increased hypothalamic-cortical discharges, of the cortex,* provided that the sino-aortic nerves were intact. Apparently the baroreceptor reflexes contribute to the homeostasis of the hypothalamus, since they counteract the changes in excitability which are associated with variations in the blood pressure. The homeostatic action of these reflexes is not confined to maintaining the level of the blood pressure within narrow limits, a function already attended to by the medulla oblongata* (154, 155, 164), but comprises the hypothalamic-cortical system and thereby the whole cerebral cortex. The great increase in psychomotor reactivity when the pressure in the carotid sinus is lowered and the sleeplike condition resulting from an increase in this pressure (197) find thus their physiological explanation.†

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*See Chapter 7, Section E.

The mechanism of this homeostatic action is more complex than has been indicated thus far. Heymans *et al.* (55, 156, 157, 160, 161, 165, 233) have shown that noradrenaline and adrenaline induce a contraction of the isolated carotid sinus preparation. This contraction raises the intramural tension and thereby stimulates the baroreceptors so that their rate of discharge increases (207) and a reflex hypotension results.‡ In addition, noradrenaline and particularly adrenaline have a blocking action on central synapses (219). Consequently, any increase in the circulating blood either of noradrenaline or adrenaline, or any increase in the concentration of noradrenaline in the wall of the carotid sinus during sympathetic stimulation, evokes homeostatic mechanisms which tend to maintain the blood pressure and the excitability of the cerebral cortex within relatively narrow limits.

If the excitation of the autonomic nervous system is confined to the sympathetic nerves, the homeostatic control of the hypothalamic-cortical system is accomplished through the baroreceptor reflexes. In intensive sympathetico-adrenal discharges, however, the medullary secretion aids in homeostasis, as we have just seen. In contradistinction to the view of Cannon, who emphasized the synergistic action of the neurogenic and hormonal factors, we believe that the neurohumors are chiefly of importance as a contributor to homeostasis.**

A brief comment on hypothalamic-medullary interrelations should be made at this time. Our experiments have shown that baroreceptor reflexes are significantly altered after lesions in the hypothalamus.

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* The baroreceptor reflexes act reciprocally on the parasympathetic and sympathetic divisions of the hypothalamus and medulla oblongata. This reciprocity contributes to their effectiveness in achieving homeostasis.

† The same mechanism is responsible for the changes in convulsive reactivity seen in different postures (130).

‡ The elimination of the chemoreceptors is without effect on this hypotension.

** It is of interest to call attention to the extensive studies of Celander (43) showing that the adrenomedullary hormones in physiological concentrations do not contribute significantly to the sympathetic effects on blood vessels, iris, and nictitating membrane, as Cannon's theory requires they should. See also Chapter 3.

Sympathetic discharges are released to a lesser degree in cats with posterior hypothalamic lesions when the blood pressure is lowered, and parasympathetic discharges are lessened in response to a rise of the blood pressure after lesions in the anterior hypothalamus. The hypothalamus seems to represent the first line of defense in the maintenance of the blood pressure, the medulla oblongata the second line, and the spinal cord, still able to govern adrenomedullary secretion (186), the third line.

A weakening of the hypothalamus through intrahypothalamic injections or lesions leads to characteristic disturbances in homeostasis. If the posterior hypothalamus is involved, the blood pressure and the heart rate fall (Figs. 59, 60, 62), whereas a fall of the blood pressure in the normal animal is commonly associated with a rise of the heart rate.

The parallelism between respiratory and blood pressure responses frequently seen in reflexes and also upon intracerebral stimulation (148) contributes likewise to the maintenance of the internal environment. The decline of the blood pressure and respiratory activity following posterior hypothalamic lesions (Fig. 77) indicates further that homeostasis is interfered with: sympathetic and closely related somatic (respiratory) processes are geared to a lower level.

## B. HOMEOSTASIS AND HYPOTHALAMIC IMBALANCE

In order to understand the problem of homeostasis in states of hypothalamic imbalance it seems best to consider first the influence of physiological variations in hypothalamic excitability on the blood pressure and on cortical activity. It may be said that inherent cyclic variations in the posterior hypothalamus (255) and the reticular formation are responsible for the sleep cycle, although the state of wakefulness depends considerably on afferent impulses (21) and on the anterior hypothalamus (246), the thalamus (149), and the cerebral cortex (30). The slight fall of the blood pressure and heart rate in sleep indicates that the autonomic processes operate at a lower but constant level. Parallel changes (the appearance of spindles and delta potentials) occur in the cerebral cortex.

In following the cortical changes through the EEG in man or the corticogram in the experimental animal during varying states of awareness (from sleep to states of attention in man and in the curarized animal before and after mild afferent stimulation), one sees that the changes in the cortex are greater than those in the blood pressure. A sciatic stimulus which does not alter the blood pressure causes a distinct excitation in the cortex (23). The inhalation of carbon dioxide (in small concentrations) causes similar changes in the cortex and hypothalamus without changes in the blood pressure. These common observations suggest that the homeostatic control of the hypothalamic downward discharge is much finer than that of the upward discharge. It should be remembered that the constancy of the blood pressure is brought about by a multiplicity of baroreceptors (sino-aortic area, 146, 155; abdomen, 158, 159; and elsewhere along the arterial system, 163), which act on the medulla oblongata and, as our work showed, on the hypothalamus. On the other hand, we have, at present, no clear evidence that there are intracerebral mechanisms limiting cortical excitation in conditions not associated with gross changes in the blood pressure.* This is perhaps not surprising since it is the primary task of the cerebral cortex to respond to minimal environmental stimuli. Homeostatic mechanisms seem to come into play only when the stimulus evokes strong hypothalamic effects associated with fight and flight and corresponding changes in the blood pressure!

Let us now consider an alteration in the excitability of the hypothalamus and cortex through the inhalation of carbon dioxide, in order to determine the effectiveness of the known homeostatic mechanisms in conditions of increased sympathetic reactivity at the hypothalamic (and medullary) level. Experiments have shown that an amount of noradrenaline producing (through sino-aortic reflexes) a marked reduction in cortical and hypothalamic excitation before the administration of carbon dioxide has only a minimal effect in hypercapnia (100). An analysis of this phenomenon will be given elsewhere. Suffice it to state that a homeostatic mechanism which reduces hypothalamic and cortical excitability in the curarized cat becomes less effective when the excitability of these structures has been increased by the inhalation of carbon dioxide.

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* In a previous book (95, pp. 400ff) I have discussed hypothalamic-cortical relations from the point of view of homeostasis and called attention to the fact that cortical depression releases the hypothalamus, increases hypothalamic-cortical discharges, and thereby contributes to the restitution of cortical function. It undoubtedly does so; but at present we are concerned with the question whether minor and therefore more physiological changes in cortical excitation can be restrained through an intracerebral mechanism. The cortical suppressor areas might serve homeostasis, as I tried to show in earlier investigations (11, 56, 88). In view, however, of the divergent opinions concerning the existence of the suppressor areas and cortical suppressor points (231, 283, 295, and, in contrast to these papers, 177), any further discussion is omitted. Attention is called to the interesting investigations of Jung and Baumgartner (187), who found through the study of individual neurons of the visual cortex under the influence of optical stimuli a local homeostatic mechanism in the cortex. Their investigations, however, throw no light on the important problem of whether special mechanisms exist which keep the intensity of the hypothalamic-cortical discharge within certain limits.

Mecholyl tests performed on young persons have shown that, particularly among psychopaths and schizophrenes, the number of those having an increased sympathetic hypothalamic reactivity is much larger than in a control group. It is suggested that repeated emotional excitement, given certain predisposing factors such as constitution, may have a cumulative effect, since no homeostatic mechanisms are known which would prevent the development of a state of increased sympathetic hypothalamic reactivity.

If, on the other hand, the sympathetic hypothalamic excitability is low, as in a certain percentage of young schizophrenes, emotional excitement and other conditions of stress are apt to evoke fewer neurogenic discharges and to increase the adrenomedullary secretion. This would in turn have a tendency further to decrease hypothalamic excitability and hypothalamic-cortical discharges.* The fact that the secreted adrenaline not only inhibits the sympathetic "centers" but also enhances the adrenomedullary secretion by action on the adrenal medulla (227–230) increases this imbalance further. The positive feedback between the hypothalamus and the cortex † must also contribute to the enhancement of the hypothalamic imbalance in conditions of sympathetic hyporeactivity and hyperreactivity.

Since, according to our analysis, states of hypothalamic imbalance tend to become aggravated through the development of vicious cycles, the search for further mechanisms that may aid homeostasis is urgent. It was thought that the effectiveness of the thalamic or caudate inhibitory apparatus, which under certain conditions of stimulation evokes spindles in the cortex and is thereby opposed to the excitatory cerebral action of the reticulo-hypothalamic system, might parallel the state of excitation of the latter, but the opposite was found to be true. The inhibitory action of the caudate nucleus does not seem to contribute to cerebral homeostasis in hypothalamic imbalance. ‡

The experiments on tuning have shown that states of sympathetic hyperreactivity are followed by a period of hyporeactivity before the autonomic balance is re-established. These slow swings in excitability serve homeostatic ends, but they can hardly be considered effective homeostatic mechanisms for the cerebral cortex. Whether such mechanisms exist, only further investigations will tell. Perhaps the great adaptive value of high cortical responsiveness made, teleologically speaking,* the development of such homeostatic controls undesirable. The long persistence of experimental neuroses (4, 5), which are commonly associated with autonomic disturbance (84), and the low restitutive capacity in the functional psychoses† might be related to such a deficiency in physiological mechanisms.‡

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* As in our physiological experiments in which repeated hypothalamic stimulation distributed over several hours resulted in a decrease in hypothalamic excitability and a change in the N/A quotient in response to various stimuli (see Chapter 3, Section E).

† See Chapter 7, Section F.

‡ See Chapter 13.

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* "Die Teleologie ist eine Dame, ohne die kein Biologe leben kann. Er scheut sich jedoch, sich mit ihr in der Öffentlichkeit zu zeigen" (Ernst Brücke). See also the extensive discussion by von Uexküll (303, 304).

† Von Uexküll calls attention to the fact that the autonomic changes in nausea and circulatory collapse (182, 211) may be looked upon as adjustment reactions to protect the heart while the response to environmental stimuli is decreased or lost. Homeostatic reactions may occur at a lower level and preserve life in conditions of maximal disturbance of supraspinal functions.

‡ The intensity of the proprioceptive discharges — of such great importance for the reactivity of the hypothalamus, as we have emphasized repeatedly — can be regulated by intracerebral structures. Granit (135) showed that stimulation of the internal capsule inhibited, and stimulation of the inferior colliculus augmented, discharges from the muscle spindles. Hagbarth and Kerr (137), in an important investigation, showed that after stimulation of a posterior root, the dorsal root reflex and the postsynaptic potentials recorded in the ventral and dorsal columns of the spinal cord were depressed by stimulation of the reticular formation and various cortical areas. It will be the task of further work to investigate whether *physiological* variations in cortical activity are associated with appropriate changes in the afferent discharges, and to determine the limitations of such a homeostatic mechanism.

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# *SUMMARY AND CONCLUSIONS*

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# SUMMARY AND CONCLUSIONS

ONE of the chief problems dealt with in this book, experimentally and clinically, is how hypothalamic functions and the state of hypothalamic balance can be evaluated in the intact organism by methods applicable to the human patient. Before this problem could be attacked, it was necessary to investigate the laws of interaction of two stimuli acting on either the parasympathetic or the sympathetic nervous system under a variety of conditions.

The blood pressure, the heart rate, and the contraction of the normal and denervated nictitating membrane served as indicators of autonomic reactivity in most of the experiments. In a smaller group the responsiveness of the bladder, duodenum, and respiration was studied in addition.

1. The laws of summation based on experiments on curarized cats are as follows:

*a.* If two stimuli are applied to central sympathetic structures such as the posterior hypothalamus, the sympathetic effect is greater than corresponds to the algebraic summation. This is true whether the stimuli are below or above the threshold. Similar results are obtained if the sympathetic nervous system is excited by the stimulation of two afferent nerves or by a combination of stimuli, one acting directly on a central structure, the other activating the central nervous system via afferent nerves. The effect of sympathetic summation may appear on any or on all of the indicators.

*b.* Similar results were obtained in investigations on the parasympathetic nervous system in which the fall of the blood pressure and the slowing of the heart rate indicated the intensity of the parasympathetic discharge. Here again electrical stimulation of the hypothalamus and of afferent nerves was employed, but parameters of stimulation were chosen that elicited parasympathetic effects. It was also shown that the parasympathetic reflex slowing of the heart rate induced by a rise of the blood pressure (for instance through noradrenaline) summates with a parasympathetic effect produced by the appropriate stimulation of either the hypothalamus or the sciatic nerve.

2. The laws of summation explain the experimental results obtained

under conditions of "reflex tuning" in the autonomic nervous system. We speak of sympathetic and parasympathetic reflex tuning when the autonomic balance in the organism (in part or as a whole) is shifted to the sympathetic and parasympathetic systems respectively. Such a shift can be accomplished, as in our experiments, by lowering the blood pressure with acetylcholine, mecholyl, or histamine, or by raising it with noradrenaline. The changes in the baroreceptor reflexes thus produced elicit a shift to the sympathetic side in the hypotensive tests and to the parasympathetic side in the noradrenaline experiment. Sympathetic discharges are consequently increased in a state of sympathetic tuning, and parasympathetic discharges in a state of parasympathetic tuning. Therefore—and this was found in many experiments—a sympathetically acting test stimulus is more effective in the state of sympathetic tuning than under control conditions: this result seems to be based on the summation of the effect of the test stimulus with the central discharge increased in sympathetic tuning.

The greater effectiveness, in a state of parasympathetic tuning, of parasympathetically acting stimuli, demonstrated in numerous experiments, is similarly explicable.

3. The law of reciprocal innervation remains valid in states of a reflexly altered imbalance of the autonomic system. Thus the responsiveness to parasympathetic stimuli is decreased in sympathetic tuning, that to sympathetic stimuli is decreased in parasympathetic tuning.

4. Immediately after the application of a sympathetically acting stimulus, parasympathetic reflexes were found to appear abruptly. Thus stimulation of the posterior hypothalamus caused an increase in the heart rate during, but a decrease after, the stimulation. This phenomenon we have named "successive autonomic induction." It is increased during parasympathetic tuning and diminished or abolished during sympathetic tuning.*

5. Parasympathetic tuning may reverse the action of hypothalamic stimulation on the blood pressure. Whereas under control conditions a pressor effect often appears during and after stimulation of the posterior hypothalamus, under conditions of parasympathetic tuning the effect may be absent during stimulation and replaced by a distinct fall of the blood pressure immediately after it. The analysis suggests that summation processes account for this result. A sympathetic hypothalamic stimulation actually elicits sympathetic *and* parasympathetic effects, although the latter are ordinarily obscured owing to the dominance in the normal organism of the sympathetic system. Under con-

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* Successive autonomic induction seems to be analogous to the "rebound" phenomenon described by Sherrington for the somatic nervous system.

ditions of parasympathetic tuning the parasympathetic component of the stimulus becomes more effective, and the sympathetic component less so: a parasympathetic reaction, the reversal of the blood pressure effect that was seen in the control, occurs.

6. The alteration in autonomic responsiveness characteristic in states of sympathetic tuning (induced by the action of hypotensive drugs) and in states of parasympathetic tuning (induced by the action of hypertensive drugs) is abolished by sino-aortic denervation. The tuning produced by these drugs in the normal organism is, therefore, the result of variations in the intensity of sino-aortic baroreceptor reflexes.

7. An increase or decrease in baroreceptor reflex activity induced by the pressor or depressor effects which occur on stimulation of the hypothalamus or on excitation of the afferent nerves leads likewise to significant changes in the reactivity of the autonomic nervous system. Thus the sympathetic effectiveness of a hypothalamic stimulus is greatly reduced if the stimulus is applied during the hypertensive phase produced by another (hypothalamic or afferent nerve) stimulus. This limitation of sympathetic discharges does not take place if the same stimuli are applied after sino-aortic denervation. Apparently a marked increase in the blood pressure and therefore in the pressure of the sino-aortic area tends to limit the sympathetic responsiveness regardless of whether the pressor effect is of peripheral origin (injection of noradrenaline) or central origin (hypothalamic stimulation). If, on the other hand, the blood pressure is lowered by a parasympathetic reflex (elicited by stimulation of the sciatic nerve with relatively low frequencies), the responsiveness of the sympathetic division of the autonomic nervous system is increased. This result seems to be analogous to the sympathetic tuning produced by the injection of hypotensive drugs.

8. The responsiveness of the sympathetic nervous system is increased after hemorrhage, and that of the parasympathetic is increased after dextran (which raises the blood pressure and the pulse pressure). These findings further illustrate states of sympathetic and parasympathetic tuning respectively, and the previously described rules apply to them.

9. The mammalian organism shows a dominance of the sympathetic system under physiological conditions and a tendency to preserve this dominance under a variety of experimental conditions. After a state of parasympathetic tuning has been induced experimentally, a phase of sympathetic tuning occurs before the physiological autonomic balance is re-established.

10. Asphyxia alters autonomic responsiveness, in part through chemo-

receptor reflexes, in part through the direct action of the altered internal environment on the central autonomic structures. If administered for brief periods, it results in a state of sympathetic tuning: hypothalamic or sciatic stimulation exerts a greater sympathetic action, and the return of the blood pressure from the drug-induced hypotension is accelerated whereas parasympathetic reflexes are diminished. If the baroreceptor reflexes are eliminated by sino-aortic denervation, the accelerated return of the blood pressure from the induced hypotension (acetylcholine test) disappears but the increased sympathetic responsiveness to stimulation of the posterior hypothalamus is retained. In asphyxia, therefore, the former effect is due to the increased effectiveness of the baroreceptor reflexes and the latter to the augmented responsiveness of the central autonomic structures.

After prolonged asphyxia a sympathetico-adrenal discharge is associated with the readmission of air. In the initial phase of this discharge, accompanied by a rapid rise of the blood pressure, a state of sympathetic tuning prevails. This phase is followed by a prolonged period during which the blood pressure remains elevated. Appropriate tests indicate that a state of parasympathetic tuning exists. Here again a state of sympathetic tuning is followed by one of parasympathetic tuning before the physiological autonomic balance is regained.

11–14. These four sections summarize the experiments which have led to the establishment of tests by which the state of the parasympathetic and sympathetic divisions of the hypothalamus can be evaluated in the intact organism.

11. Hypotensive drugs (mecholyl, acetylcholine, and histamine elicit a sympathetic discharge, indicated by the contraction of the nictitating membrane and the acceleration of the heart rate. If these sympathetic discharges are strong, the return of the blood pressure from hypotension to the control level is quick and is followed by a hypertensive phase; if, on the other hand, the sympathetic discharges are weak, the return of the blood pressure from the hypotension is delayed.

These observations suggest that, other conditions being equal, the return of the blood pressure from the drug-induced hypotension is a measure of central sympathetic excitability. Extensive experimental work has proved, indeed, that the size of the hypotensive area* is determined by the excitability of the sympathetic division of the hypothalamus. This conclusion is based on the following observations:

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* The hypotensive area produced by the action of the above-named drugs is determined by the initial blood pressure, the maximum of the hypotensive effect, and the slope of the blood pressure curve leading back to the original level. Since the last is the chief variable in different experimental conditions, an increase or a decrease of the hypotensive area signifies a delayed or an accelerated return of the blood pressure respectively.

*a.* If drugs such as metrazol or strychnine are injected into the posterior hypothalamus, they raise its sympathetic responsiveness to electrical stimulation and alter the action of hypotensive drugs considerably: the hypotensive area decreases, and the hypotensive phase is frequently followed by a hypertensive phase. At the same time the hypotensive drug elicits greater sympathetic discharges, indicated by the acceleration of the heart rate and the contraction of the nictitating membrane.

*b.* If drugs such as pentothal or procaine are injected into the posterior hypothalamus, they lessen its sympathetic responsiveness to electrical stimulation and also intensify the action of hypotensive drugs: the hypotensive area increases; the return of the blood pressure is delayed and often incomplete. The associated signs of sympathetic discharges which accompany the hypotensive action are greatly diminished.

The experimental results described in paragraphs *a* and *b* are reversible.

*c.* Mild degrees of excitation of the sympathetic division of the hypothalamus are associated with a decrease in the hypotensive area produced by mecholyl and related drugs. This effect may be accomplished by subthreshold or threshold stimulation of the posterior hypothalamus or by the inhalation of carbon dioxide (6 to 10 per cent). As in the experiments listed under *a,* the sympathetic responsiveness of the hypothalamus to electrical stimulation is increased under these conditions and the sympathetic discharges accompanying the action of the hypotensive drugs are augmented.

*d.* During spontaneous arousal reactions, known to be associated with an increased excitability of the posterior hypothalamus, the action of hypotensive drugs is lessened. The records are similar to those described under *c,* as if the posterior hypothalamus had been stimulated.

*e.* Bilateral lesions, produced by high-frequency currents and confined to the posterior hypothalamus, aggravate the action of hypotensive drugs. Except that the effects in these experiments are not reversible, they are similar to those obtained through the reduction of sympathetic hypothalamic excitability by the intrahypothalamic injection of pentothal or procaine.

12. The relation of a parasympathetic reflex to the anterior hypothalamus was explored in a similar manner. The reflex chosen was the

slowing of the heart rate induced by the pressor action of noradrenaline.

The injection of pentothal into the anterior hypothalamus (between the anterior commissure and the optic chiasma) led to a marked and reversible reduction of the pulse slowing. This reduction of the parasympathetic reflex occurred even in cases in which the noradrenaline-induced pressor effect was increased. Similar effects were produced by bilateral coagulations in the anterior hypothalamus, except that the drug action on the hypothalamus was reversible and that of the coagulation was not.

13. The autonomic balance of the hypothalamus was investigated by testing the action of noradrenaline *and* mecholyl (or other hypotensive drugs) before and after hypothalamic lesions. It was found that lesions of the posterior hypothalamus lead not only to diminished sympathetic reflexes (indicated by the mecholyl test) but also to increased parasympathetic reflexes (noradrenaline test). Conversely, lesions of the anterior hypothalamus produce, in addition to the diminution of parasympathetic reflexes, an increase in sympathetic reflexes. The principle of reciprocal innervation is, therefore, valid for sympathetic-parasympathetic relations at the hypothalamic level.

14. The diencephalon exerts a tonic sympathetic and parasympathetic function through, respectively, the posterior and anterior divisions of the hypothalamus. Lesions of the posterior hypothalamus lead to a gradual fall of the blood pressure and heart rate, whereas lesions of the anterior hypothalamus cause a rise of the blood pressure and an acceleration of the heart rate. From these experiments and similar work concerning the action of intrahypothalamically injected drugs on tonic autonomic discharges it is inferred that tonic parasympathetic and sympathetic discharges from the anterior and posterior hypothalamus are directly related to the degree of excitability of these areas.

If in cases of low and high sympathetic hypothalamic excitability the mecholyl* test is performed, the sympathetic discharges released from autonomic central structures through lessened baroreceptor reflexes summate with these tonic discharges. Consequently, the total sympathetic discharge increases with increasing sympathetic hypothalamic excitability, and this increase in the discharge accounts for the quicker return of the blood pressure in cases of sympathetic hyperreactivity. This summation process (similarly applied to the slowing of the heart rate caused by noradrenaline) appears to be the mechanism by which the noradrenaline-induced parasympathetic reflex and the mecholyl-induced sympathetic reflex become indicators of autonomic hypothalamic excitability and balance.

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* For the sake of brevity the term mecholyl is used instead of mecholyl, acetylcholine, or histamine.

15. Analogous experiments were performed in order to investigate the influence of hypothalamic lesions on the level of respiratory activity. This influence corresponded to the tonic vascular effects described in Section 14. Posterior hypothalamic lesions resulted in a diminution of respiratory activity, anterior hypothalamic lesions in an increase (in amplitude and/or rate of respiration).

The investigation of phasic respiratory reflexes was confined to the posterior hypothalamus. It was found that the reflex excitation of respiration caused by the stimulation of afferent nerves or by asphyxia was lessened when by the injection of pentothal into the posterior hypothalamus or by coagulation in this area the sympathetic hypothalamic excitability was reduced. On the other hand, the effectiveness of inhibitory respiratory reflexes (Hering-Breuer reflex) was increased under these conditions.

It is inferred from this work that the hypothalamus provides tonic impulses to the vascular and respiratory systems. Moreover, the excitability of the hypothalamus determines to an important degree the intensity (and the threshold) of the reflex responses which were generally thought to be of medullary (and pontine) origin.

16. Further studies provide a basis for a more detailed analysis of the sympathetic "downward discharge," its relation to various types of emotion, and its influence on the action of hypotensive drugs as employed in the mecholyl test.

*a.* It is shown that under the influence of increasing hypothalamic excitation the downward discharge passes through the following stages: (1) partial sympathetic discharge; (2) generalized sympathetic discharge; (3) generalized sympathetico-adrenal discharge (the hormonal discharges being indicated by the contraction of the denervated nictitating membrane). The transition from the second to the third stage may be accomplished also through summation processes involving in part direct and in part reflex excitation of the autonomic central structures; it may also result from the application of a mild stimulus in a condition of heightened sympathetic responsiveness such as asphyxia.

*b.* Quantitative investigations of the three stages of sympathetic discharge on normal and denervated pupils and nictitating membranes give no evidence that the neurogenic sympathetic discharges are reinforced by adrenomedullary secretion. In general, there is a rather sharp temporal separation between the neurogenic and the hormonal phase; moreover, an adrenomedullary secretion leading to a maximal dilatation of the denervated pupil and to a complete contraction of the denervated nictitating membrane is accompanied by a rapid constriction of the normal pupil and a relaxation of the normal nictitating membrane. These observations suggest that the adrenomedullary secretion inhibits the neurogenic discharge. The following experiments have verified this assumption.

*c.* The hypotensive action of mecholyl and similar drugs is lessened during a neurogenic discharge but aggravated during an adrenomedullary secretion provided that the latter is associated with little or no neurogenic discharges.* Similarly, the effect of sympathetic hypothalamic stimulation is increased during a neurogenic sympathetic discharge (see Section 1*a* of this summary) but lessened during adrenomedullary secretion. It may, therefore, be said that the excitability of the sympathetic system to stimuli acting directly on the sympathetic division of the hypothalamus or affecting it reflexly (as in the mecholyl test) is diminished in states of adrenomedullary secretion if this secretion occurs with no or little evidence of a neurogenic sympathetic discharge.

*d.* These findings raise the question which factors modify the ratio *Neurogenic discharges/Adrenomedullary secretion* (N/A). It was found that conditions which lower the excitability of the cerebral cortex and the diencephalon reduce or eliminate the responsiveness of the neurogenic sympathetic discharges without interfering with a considerable or even maximal adrenomedullary secretion. Thus nociception or a brief period of asphyxia produces a neurogenic response in the awake cat but elicits chiefly an adrenomedullary effect during anesthesia. Since the neurogenic response leads to sympathetic tuning and the adrenomedullary secretion to a damping of the reactivity of the sympathetic system and to a state of parasympathetic tuning, any change in the ratio N/A is of fundamental importance for the reactivity of the autonomic nervous system.

*e.* For physiological changes of the N/A ratio proprioceptive impulses, which have been shown to act on the posterior hypothalamus, seem to be of particular importance. A diminution of these impulses lowers hypothalamic sympathetic excitability and, in correspondence with this change, the N/A ratio in response to stimuli or conditions, such as asphyxia, evoking a sympathetic effect. After the administration of curare-like drugs in awake cats, a loss in aggressiveness and an increased tendency toward escape reactions also result. It is suggested that emotional states like anger and resentment, associated with an increased tone of the muscles, have a tendency to produce a sympathetic discharge with a higher N/A ratio than states of fear and terror, in which the tone of the muscles is probably minimal.

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* Such a neurogenic response is measured by the degree of contraction of the normal nictitating membrane, whereas the adrenomedullary secretion is gauged by the degree of contraction of the denervated nictitating membrane.

17. In a group of experiments the hypothalamus was stimulated at various intensities, and the effects on the gut and bladder and on the blood pressure, heart rate, and nictitating membrane were recorded. Whereas under moderate intensities of stimulation the blood pressure, heart rate, and gut yielded sympathetic effects (loss of tone and decrease in the height of the contractions), the increased activity of the bladder revealed that this organ was in a parasympathetic state. Only under more intensive stimulation leading to a sympathetico-adrenal discharge did bladder and gut show sympathetic effects at the same time. These effects corresponded in degree and duration with the contraction of the denervated nictitating membrane and may, therefore, be considered to have been due to the action of the adrenomedullary hormones.

The fact that the effects on the heart rate, blood pressure, and gut were sympathetic while those on the bladder were parasympathetic shows the limitations of centrally induced sympathetic discharges. It is inferred that in states of sympathetic tuning not all organs are affected in a similar manner. The clinical importance of this finding is emphasized.

Further studies on the influence of the hypothalamus on the gut showed that the sympathetic (inhibitory) effects are often followed by a parasympathetic phase in which the tone and activity of the gut are increased. The intensity of this delayed and often prolonged reaction increases with the intensity of the stimulus and the degree of the sympathetic response. The dependence of this reaction on a strong sympathetic responsiveness of the hypothalamus suggests that such parasympathetic reactions appear more frequently in emotional states like anger and resentment than in those of fear and terror; in the latter group (in contrast to the former) there is no proprioceptive reinforcement of the hypothalamic reactivity and consequently the N/A ratio of the sympathetic discharge is likely to be low.

18. It was shown earlier in the writer's laboratory that any excitation of the posterior hypothalamus (directly or reflexly) caused a diffuse hypothalamic-cortical discharge, associated with an arousal reaction. Among the sensory modalities which have been tested the following sequence corresponding to an increasing effectiveness in evoking a

hypothalamic-cortical discharge has been found: visual, auditory, proprioceptive, and nociceptive. Unilateral lesions in the posterior hypothalamus reduce or, in the case of near-threshold stimuli, abolish the excitatory action of nociceptive stimuli.

The significance of this hypothalamic-cortical discharge lies in the fact that it modifies the responsiveness of the cerebral cortex to afferent and efferent stimuli. Action potential studies indicate that subthreshold afferent stimuli (optic or acoustic) become effective under the influence of a hypothalamic-cortical discharge. Moreover, stimulation of the posterior hypothalamus augments the discharges which are recorded in the pyramidal tracts at the medullary level.

If the excitability of the posterior hypothalamus is increased by the inhalation of 10 per cent carbon dioxide or if it is lowered by the inhalation of 35 per cent carbon dioxide, by the action of barbiturates, or by a lowering of the temperature of the body, corresponding changes in the intensity of the hypothalamic-cortical discharges ensue. Corresponding effects are noted when the hypothalamic balance is altered by the injection of pentothal or metrazol into the posterior hypothalamus. It is concluded that changes in the excitability of the hypothalamus and alterations in the hypothalamic balance produce parallel changes in the sympathetic downward discharge and the hypothalamic-cortical discharge. The direction and degree of change in these discharges are directly related to the excitability of the posterior hypothalamus.

19. In view of the fact that hypotensive and hypertensive drugs alter the responsiveness of the posterior hypothalamus to electrical stimulation through baroreceptor reflexes, their relation to the hypothalamic-cortical system was investigated.

Hypotensive drugs, it was found, elicit a diffuse excitation of the cortex. Unilateral lesions of the posterior hypothalamus reduce this action on the ipsilateral cortex. By means of a frequency analysis of the cortical potentials it was shown that the diffuse excitation of the cortex associated with a hypotensive action is abolished by sino-aortic denervation. The frequency analysis of the hypothalamic potentials showed also an excitation of the posterior hypothalamus during a drug-induced hypotension.

Hypertensive drugs (noradrenaline) exert the opposite effect on the cortex if administered in small doses. Grouped potentials (as in sleep) appear, and a frequency analysis reveals an increase in the amplitude of the integrated potentials of low frequencies. This effect is abolished (or reversed) by sino-aortic denervation.

If the blood pressure is decreased by alterations in the blood volume

(Fog's apparatus), the cortical potentials are changed as in the experiments involving hypotensive drug action.

It is concluded that baroreceptor reflexes act on the posterior hypothalamus and influence cortical activity via the hypothalamic-cortical system. A fall of the sino-aortic pressure leads to an excitation of the posterior hypothalamus and increased diffuse cortical discharges, whereas an increase in this pressure has the opposite effect.

20. The work of Murphy and Gellhorn, Bremer, and others has shown that the hypothalamus and the reticular formation receive excitatory impulses from the cerebral cortex. These impulses enhance the excitability of the posterior hypothalamus and thereby increase the intensity of the hypothalamic-cortical discharges. If strychnine is topically applied to a site of the cerebral cortex and the potentials are recorded from several sites of this area, the variations in the intensity of the focal convulsive discharges and in the size of the cortical area involved may be taken as an indicator of the degree of the corticofugal discharges. On the basis of this criterion it was found that the corticofugal discharges are enhanced in states of hyperexcitability of the posterior hypothalamus and diminished by the injection of pentothal into this structure.

Behavioral disturbances that accompany states of hypothalamic imbalance may be related to the quantitative and qualitative alterations that must occur in the cortico-hypothalamic and hypothalamic-cortical discharges, as the experimental work presented in this section shows, in these pathological conditions.

21. In order to investigate the principles that should guide the restitution of function in cases of hypothalamic autonomic imbalance, a series of experiments was performed on the action of drugs under these conditions. It was found that conditions of hypothalamic imbalance produced by the injection of pentothal, strychnine, or metrazol into the posterior hypothalamus can be offset by appropriate drugs. Thus a hypothalamic sympathetic hyporeactivity is eliminated by metrazol in subconvulsive doses or by desoxyn; a hypothalamic sympathetic hyperreactivity is offset by barbiturates.

The action of barbiturates and chlorpromazine was also studied. On unanesthetized cats with chronically inserted electrodes in the hypothalamus these drugs reduce hypothalamic sympathetic and behavorial responses, but chlorpromazine is much less effective than pentothal. Action potential studies indicate that neither of the drugs is specific for the hypothalamus, that they depress first the cortex and then the diencephalon, and that between the two stages a brief phase occurs during which the hypothalamus seems to be excited (release from cortical inhibition). In effective doses both drugs diminish the parasympathetic pulse-slowing reflex and aggravate the hypotensive effect of mecholyl and related drugs, results indicating that anterior and posterior hypothalamic functions are depressed.

22. In addition to the diffuse excitatory action on the cerebral cortex of the posterior hypothalamus and the reticular formation, inhibitory effects can be obtained by stimulation of the intralaminar (and other related) nuclei in the thalamus and by stimulation of the caudate nucleus. The effect of stimulating the caudate nucleus was therefore investigated in a variety of experimental conditions which lead to changes in the excitability of the posterior hypothalamus.

Conditions which increase the activity of the posterior hypothalamus (spontaneous or induced arousal, inhalation of carbon dioxide, rise of the temperature of the body) raise the threshold for eliciting the inhibitory (recruiting) response from the caudate nucleus. Conversely, conditions which lower the activity of the posterior hypothalamus (lowering the temperature of the body, drowsiness, sleep, or anesthesia) lower the threshold for the recruiting response. Pharmacological experiments with metrazol on the one hand and barbiturates, chlorpromazine, and panparnit on the other confirm these conclusions. The great importance of the hypothalamus for the recruiting response is indicated by the following facts: (a) Coagulation of the posterior hypothalamus or the injection of pentothal into this structure eliminates the effect of variations in body temperature and of carbon dioxide on the recruiting response. (b) Pentothal, which is known to block the reticulo-hypothalamic-cortical system in small concentrations, eliminates the effect of metrazol on the threshold of the recruiting response induced by the caudate nucleus. From these investigations it appears advisable to restore imbalances of the hypothalamus through procedures acting on the hypothalamic-cortical system and not through any influencing the caudate nucleus.

23. In order to investigate the autonomic reactivity of the hypothalamus in man, tests were performed on numerous normal persons and on persons who were psychiatric cases.

The mecholyl test as used by Funkenstein was found to be superior to other hypotensive drugs. Its action is reproducible when an injection is repeated after an interval of days or weeks. Certain quantitative criteria were described for dividing subjects into three groups: first, the sympathetic hyperreactors, in whom the mecholyl blood pressure curve shows a hypertensive phase following a brief hypotensive phase; second, the intermediate group, representing "normal" sympathetic responsiveness, in whom the original blood pressure level is reached after about 8 to 10 minutes; third, the sympathetic hyporeactors, in whom the mecholyl curve shows a prolonged hypotensive phase. Applied to controls and to neuropsychiatric cases, the test showed that sympathetic reactivity as determined by the mecholyl reaction decreases with increasing age. This influence of age is so considerable that a comparison of "normal" with "abnormal" persons is valid only if groups of similar ages are compared.

At the age of 25 years or younger the intermediate group represents about 70 per cent of the normals and 30 per cent of the abnormals. The sympathetic hyper- and hyporeactors predominate in the group of mental cases but are in the minority in the control group. This dominance of hyper- and hyporeactors in the abnormal group as well as the dominance of the intermediate reactors in the control group is retained at other age levels, but the hyperreactors decline in favor of the hyporeactors with increasing age.

The groups of persons diagnosed as schizophrenics and psychopathic personalities respectively were tested in sufficient numbers to permit a comparison between the two groups at similar ranges of age. It was found that the hyperreactors are more numerous among the psychopaths than among the schizophrenics and that at the young age (25 years or less) the hyporeactors are absent among the psychopaths and normals but present among the schizophrenics.

It is suggested that psychiatric therapy be directed toward restitution of the normal sympathetic hypothalamic reactivity.

Parasympathetic reactivity was investigated in the controls and in the neuropsychiatric series by testing the pulse-slowing reflex following the intravenous injection of 0.005 mg. of noradrenaline. The quotient *Maximal rise of the blood pressure/Maximal diminution of the heart rate* was determined. It is inversely related to the parasympathetic reflex reactivity. These quotients varied widely in both groups so that no characteristic difference between them in parasympathetic reactivity could be found. However, both groups showed a decrease in parasympathetic reactivity with increasing age, the effect being less in the psychiatric group. Furthermore, in the control group parasympathetic reactivity increased with an increasing initial pulse rate, an effect which was absent in the clinical group. These data suggest that parasympathetic reactivity is lessened in the clinical group, but much more work is necessary to establish the relation between parasympathetic reactivity and mental disease.*

* See also footnote on p. 237.

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# *EPILOGUE*

It isn't simple at all. . . . It's desperately complicated. But at the end there's light.

J. Steinbeck, *East of Eden*

Das Ziel sehe ich. Wenn ich auf dem Wege liegen bleibe—so hoffe ich, werden ihn meine jungen Weggenossen, meine Schüler zu Ende gehen. (I see the goal. If I fall along the way, my fellow travelers, my students, will, I hope, pursue it to the end.)

W. Dilthey, *Die geistige Welt* (Berlin, 1924)

A grain of slightly mad recklessness might, in this domain as in others, be the price you have to pay for great and noble findings.

C. Levi-Strauss, in *Diogenes*, 1954 (p. 108)

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# EPILOGUE

AFTER the facts and their interpretation have been presented and an attempt has been made to show the significance of the experimental work on which this monograph is based, several questions of fundamental interest require a brief discussion. They are relegated to this last section and thereby separated from the experimental and critical parts because a somewhat personal attitude appears to be unavoidable. Whereas I have striven to report the experimental data objectively and to draw only such conclusions as appear warranted by the facts, I feel that some larger questions cannot be handled in this way.

One of these questions, important and all-embracing, concerns the psychophysiological relation. It is obvious that this topic, which has occupied the minds of philosophers for two thousand years, cannot adequately be dealt with in a few lines. But it is not the causal, parallelistic, or any other relation that may exist between so-called psychic events and the material processes going on in the brain that is the question primarily concerning the neurophysiologist. Even if he readily admits that du Bois-Reymond's (58) famous "ignorabimus" and Sherrington's (281) skepticism, forcefully expressed in his Rede lecture, are still valid in this respect, he is not completely blocked in the attempt to bring the newer neurophysiological knowledge to bear upon the problems of the mind. It may be conceded at the outset that human thought and emotion will never be understood in terms of action potentials, polarization, or metabolic cerebral processes—a truism if one remembers that the infinitely more malleable tool of human language, forged by Homo sapiens in the course of untold generations and refined by creative writers for several thousand years, is hardly able to do more than to mirror the complexity of human feelings. But this admission does not prevent the neurophysiologist from contributing to the elucidation of the essential mechanisms underlying such fundamental psychic processes as consciousness and sensation and perception.* Through these investigations a rough outline is available of some physiological processes which are necessary (although not sufficient) to produce or eliminate general awareness or a specific sensation.

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* On the physiology and pathology of consciousness, see the chapters so titled in item 94, pp. 181–228; on sensation and perception, see item 97 for a survey of the problem and items 122 and 123 for more detailed studies.

It is possible to produce experimentally sleep (149), coma (214), and states of increased (315) and diminished (10) emotional responsiveness as well as a condition which symptomatically and in its electroencephalographic effects resembles a brief attack of petit mal (180, 184). These and similar observations indicate that, just as in other sections of the natural sciences the experimental method has led to a certain degree of mastery of nature, in this particular instance it has led to a mastery over psychophysiological processes.

The history of civilization shows that an incomplete knowledge of nature does not prevent man from influencing natural processes. On the contrary it seems to be characteristic that man can solve his important problems through *action* long before he can understand the underlying mechanisms. As everybody knows, Prometheus' deed, which created civilization, preceded by eons Priestley's great discovery of the nature of the process of oxidation. The psychological motivation was the urge of necessity. Does not the same situation exist today with respect to the problem of mental diseases? And is not the most appropriate basis for action our admittedly inadequate knowledge of the physiology of the brain, which nevertheless permits "psychic" events to be changed through alterations in the underlying or intimately related neurophysiological processes (although the nature of this relation is unknown and may never be known)?

That psychophysiological processes may be influenced also in man has been amply demonstrated by the clinical induction of sedation and anesthesia through drugs and by the experimental establishment of psychically abnormal states with mescaline (20) and other drugs (53, 195).

The lessened emotional response to pain observed in mentally normal persons after frontal lobotomy is a further illustration that alterations in the neurophysiological system influence psychophysiological processes. These and many similar experimental and clinical observations are convincing evidence that fundamental changes in psychophysiological behavior can be achieved by appropriate changes in the physiology of the brain regardless of whether these changes are produced through surgery, as in frontal lobotomy, lobectomy, and topectomy, or through functional alterations of the neurons, as in convulsions (electroshock, metrazol-convulsions) and in insulin coma. From the physiological point of view the following brief comment on these therapeutic endeavors may be permitted.

# *Epilogue*

In frontal lobotomy and similar operations the neurophysiological system is deprived of one of its most complex and advanced mechanisms, and the success of this operation in favorable cases seems to be related to the lesser complexity of the remaining psychophysiological activity. Although this procedure may be valuable for cases with intractable pain and for ungovernable chronic mental cases, it can hardly be called a form of therapy in *functional* disorders. Such disorders require a therapy through which, by physiological or pharmacological means, brain functions are altered and ultimately restored.

The so-called shock therapies fulfill this postulate, at least to a certain degree, if it can be assumed that the therapeutic effects are the result of functional changes produced in the brain. As pointed out earlier (86, 87, 90, 94), the different forms of shock therapy have in common this feature, that they increase sympathetic central excitability reversibly and for a considerable period of time. They seem, therefore, appropriate in functional psychoses in which hypothalamic sympathetic excitability is decreased.

These procedures are distinguished in principle from an ideal form of therapy (even if the curative effect were far greater than it is) in that convulsions and coma affect the whole brain and are not specifically directed toward those structures and functions which—at least in the theory presented in this monograph—are responsible for the therapeutic effects.

On the basis of the data presented in this work, a physiological therapy of certain forms of functional psychoses can be envisaged that would be founded on physiological tests revealing the nature of the underlying central autonomic disturbances. We obviously are still far removed from this goal, as far as functional psychoses are concerned. But a beginning, however modest, that may ultimately lead to a physiologically oriented therapy of functional psychoses, has been made. The experimental work and the clinical tests described in this monograph indicate that the autonomic excitability of the hypothalamus can be measured in man and that hypothalamic autonomic disorders and imbalances can be ascertained in certain forms of mental illness. The parallelism between the clinical recovery and the Funkenstein test suggests that autonomic hypothalamic disturbances are not a by-product but intimately related to the behavioral disturbance. The therapy, therefore, should be directed toward a restitution of the autonomic balance. Cases characterized by central sympathetic hyperfunction require a form of therapy diametrically opposed to that needed for cases of parasympathetic hyperfunction or sympathetic hypofunction.* Some experiments which may serve as experimental models for restitution in cases of experimentally induced hypothalamic autonomic imbalances have been discussed. They were not presented as suggestions for the therapy of human illness but rather as illustrations of the principle that functional hypothalamic imbalances can be corrected by functional means.

It is not assumed that the abnormal behavior observed in mental illness is the immediate effect of the disturbed hypothalamic functions that may be revealed by autonomic tests. But alterations in hypothalamic functions and autonomic imbalance, it is thought, lead secondarily to changes in the hypothalamic-cortical discharge and thereby to alterations in cortical functions. Even if this factor is admitted to be only one of many (as yet unknown) productive of the behavior disturbances seen in functional psychoses, the restoration of the hypothalamic balance and of the hypothalamic-cortical discharge may constitute the turning point in the complex processes of disease. All medical therapy, it should be remembered, is based on the faith that nature, if given a chance, will lead to improvement and, within certain limits, to recuperation.†

To add a warning may not be superfluous. In view of the decisive role which the hypothalamic-cortical discharge is believed to play in normal and abnormal behavior, it is not expected that every drug capable of shifting the autonomic balance in the desired direction under conditions of animal experimentation will be of therapeutic value. Such a drug may at the same time so alter cortical functions that the beneficial effect of the restitution of the hypothalamic autonomic balance is complicated or offset. Animal experimentation may be of great help in determining such side effects, but the main task of the neurophysiologist and pharmacologist will be to select suitable drugs or procedures for clinical trial. The clinical trials should be guided not only by the behavior of the patient but by the objective determination of the state of the hypothalamus through appropriate autonomic tests before and during the application of therapeutic procedures.

Although a greal deal of work remains to be done, I believe that a team of investigators consisting of neurophysiologists, pharmacologists, psychiatrists, and psychologists may be able to erect, on the basis of the experimentally founded outline given in this book, a solid structure which will increase our knowledge of brain functions and the physiological basis of behavior and may contribute to the therapy and also to the prevention of some functional psychoses.

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* The important work of Moriarty (239) on the action of carbon dioxide therapy seems to confirm this thesis.

† Livingston and Worden (215) after discussing the complexity of the neurological apparatus involved in the emotions, state that "a comprehensive therapeutic approach in relation to the treatment of the sick would include the possibilities of beneficial modification of this transactional mechanism by appropriate treatment *along each and every avenue of access into this system*" (italics mine).

The work described in this monograph has aimed primarily at contributing to an understanding of the general physiology of the autonomic nervous system and particularly of the physiological significance of alterations in the central autonomic balance. The similarity between the experimentally established facts and certain clinical observations has made it very tempting to apply this new knowledge to clinical problems. I realize that I have trodden on dangerous ground. No doubt my program for neuropsychiatric research and my practical suggestions* will be rejected by some as speculation or dreams. To these critics I have two answers: (1) Facts as such are sterile, and only ideas grown from well-established facts are responsible for the advancement of science. (2) History has shown that not the realists but the dreamers have conquered the world.

It is my hope that the ideas expressed in this monograph, when further applied, will result in the emergence of new facts and become, in their turn, as seems to be the way in scientific history, a seedbed for new ideas. Like every scientific worker, however, I am prepared to abandon the thought of applying the physiological principles expounded in this book to neuropsychiatric problems if carefully established facts demonstrate the approach to be unfeasible. The satisfaction derived from the work will remain unaltered; even errors may bear fruit. Moreover, as ancient wisdom puts it,

IN MAGNIS VOLUISSE SAT.

*It is sufficient to have attempted great things.*

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* For details see items 94, pp. 478ff, and 99.

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# *BIBLIOGRAPHY AND INDEX*

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